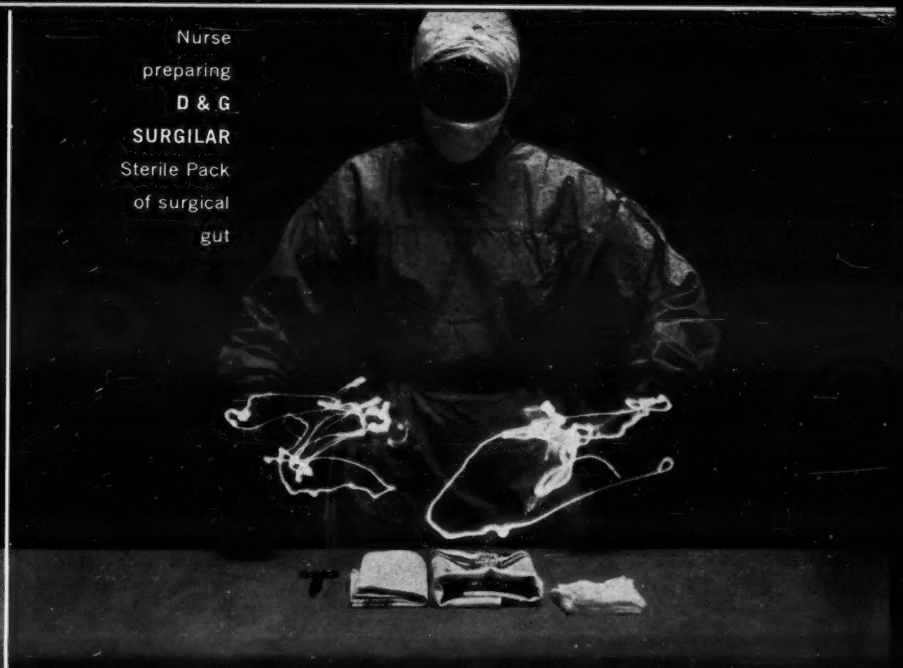
SURGERY
Gynecology & Obstetrics

WITH

INTERNATIONAL ABSTRACTS OF SURGERY

August, 1956

VOLUME 103 • NUMBER 2



Save suture handling with **D & G** **SURGILAR*** Sterile Pack

GET BROKEN GLASS OUT OF THE O. R.

Light-tracings in the time-and-motion pictures show a nurse's hands at work. Compare the simple motions she uses to prepare SURGILAR Sterile Pack of surgical gut with the many motions for tubed gut. She can handle SURGILAR ⅓ faster than tubes.

SURGILAR saves hospital nurse-power and money. It eliminates glass tubes, provides stronger, more flexible D & G surgical gut coiled in quickly opened, double, sterile transparent envelopes.

Hospital-tested SURGILAR helps to improve patient care. It keeps broken glass out of your O.R. No glass fragments to damage sutures, cut fingers, perforate gloves, or invade the operative field.

With SURGILAR, double envelopes are quickly cut, gut easily withdrawn, ready for use. No need to wash plastic envelopes after exposure, since they are protected by the outer envelopes. Jars store in ½ space required for tubed gut.

photo technic: ***light-tracings of hands to which bulbs are attached.***

D&G **hospital-tested** packaging makes the difference

DAVIS & GECK
A DIVISION OF AMERICAN CYANAMID COMPANY

SURGERY
Gynecology & Obstetrics

AUGUST 1956

VOLUME 103
NUMBER 2

CONTENTS

THROMBOCYTOPENIA AND HEMORRHAGE IN HEMOLYTIC BLOOD TRANSFUSION REACTIONS. *P. W. Pifer, M.D., M. A. Block, M.D.,* and *C. P. Hodgkinson, M.D., F.A.C.S.*, Detroit, Michigan 129

THE TREATMENT OF SELECTED CASES OF MULTIPLE POLYPS, FAMILIAL POLYPOSIS, AND DIVERTICULAR DISEASE OF THE COLON BY SUBTOTAL COLECTOMY AND ILEOPROCTOSTOMY. *Ira Teicher, M.D., F.A.C.S.,* and *Jesse I. Abrahams, M.D.*, Brooklyn, New York 136

STRUCTURAL ALTERATIONS IN HUMAN AORTIC HOMOGRAFTS ONE TO TWO AND ONE-HALF YEARS AFTER TRANSPLANTATION. *Oscar Creech, Jr., M.D., F.A.C.S., Michael E. De Bakey, M.D., F.A.C.S., Denton A. Cooley, M.D., F.A.C.S.,* and *Béla Halpert, M.D.*, Houston, Texas. 147

FREEZE-DRIED AND ALCOHOL PRESERVED HOMOGRAFTS FOR REPLACEMENT OF SMALL ARTERIES. *Thomas C. Moore, M.D., F.A.C.S., Angelo Riberi, M.D.,* and *Hisashi Kajikuri, M.D.*, Indianapolis, Indiana 155

CLINICAL SIGNIFICANCE OF CHANGES IN COMMON DUCT BILE RESULTING FROM A NEW SYNTHETIC CHOLERETIC. *John M. McGowan, M.D., B.S., M.S.(Surg.), F.A.C.S., F.R.C.S.*, Quincy, Massachusetts 163

CANCER OF THE THYROID GLAND. *Donald E. Ross, M.D., F.A.C.S.*, Los Angeles, California .. 171

SURGICAL TREATMENT OF OCCLUSIVE CORONARY ARTERY DISEASE BY ENDARTERECTOMY OR ANASTOMOTIC REPLACEMENT. *Karel B. Absolon, M.D., Joseph B. Aust, M.D., Richard L. Varco, M.D., F.A.C.S.,* and *C. Walton Lillehei, M.D., F.A.C.S.*, Minneapolis, Minnesota .. 180

MALIGNANT LESIONS OF THE NIPPLE EXCLUSIVE OF PAGET'S DISEASE. *Gordon H. Congdon, M.D.,* and *Malcolm B. Dockerty, M.D.*, Rochester, Minnesota 185

PARAPHARYNGEAL NEURILEMMOMA. *Don O. Gore, M.D., Robin Rankow, M.D.,* and *John M. Hanford, M.D., F.A.C.S.*, New York, New York 193

THE EXPERIMENTAL PRODUCTION OF THE PULMONARY EMBOLISM SYNDROME AND THE EFFECTS OF VARIATIONS OF SYSTEMIC ARTERIAL PRESSURE ON ITS COURSE. *David State, M.D., Ph.D., F.A.C.S.,* and *Peter F. Salisbury, M.D., Ph.D.*, Los Angeles, California 202

THE CHARACTERISTICS OF REGENERATION OF RESPIRATORY EPITHELIUM. *Noble O. Correll, Jr., M.D.,* and *Edward J. Beattie, Jr., M.D., F.A.C.S.*, Chicago, Illinois 209

[CONTENTS CONTINUED ON PAGE 7]

DAVIS & GECK
A DIVISION OF AMERICAN CYANAMID COMPANY
stronger, more flexible D & G surgical gut are protected by the steel envelope.
coiled in quickly opened, double, sterile Jars store in ½ space required for
transparent envelopes. tubed gut.

NEW SERA-VAC®

with Sterile Vacuum Pilot Tube

blood bottle and tube are **inseparable**—
only one label required

A major advance in blood bottle design, the unique SERA-VAC with its sterile, internal vacuum pilot tube offers these important advantages to hospitals and blood banks—

prevents errors—SERA-VAC's internal pilot tube cannot be mislabeled, interchanged, lost or broken.

saves time—SERA-VAC eliminates labeling and taping of pilot tube to bottle...one less tube to handle.

stores easily—SERA-VAC packs tightly and rotates easily for daily inspection.

improves clot retraction—SERA-VAC's pilot tube is warmed by blood around it...pilot tube blood cools more slowly.

products of

BAXTER LABORATORIES, INC.

Morton Grove, Illinois

DISTRIBUTED AND AVAILABLE ONLY IN THE 37 STATES EAST OF THE ROCKIES (except in the city of El Paso, Texas) THROUGH

AMERICAN HOSPITAL SUPPLY CORPORATION

SCIENTIFIC PRODUCTS DIVISION GENERAL OFFICES • EVANSTON, ILLINOIS

HEMODYNAMIC CHANGES RESULTING FROM BLOOD VESSEL GRAFTS AND PROSTHESES. *Worthington G. Schenk, Jr., M.D., James H. Cosgriff, Jr., M.D.*, and *James G. Gray, M.D.*, Buffalo, New York 212

A STUDY OF 531 CASES OF ENDOMETRIAL CARCINOMA. *John H. Randall, M.D., F.A.C.S.*, and *William B. Goddard, M.D.*, Iowa City, Iowa 221

BODY COMPOSITION AND BODY WATER METABOLISM IN NORMAL PREGNANCY. *Harold B. Haley, M.D.*, and *John W. Woodbury, M.D.*, Boston, Massachusetts 227

THE USE OF THE BIOFLAVONOID COMPOUNDS IN THE PREVENTION OR REDUCTION IN SEVERITY OF ERYTHROBLASTOSIS FETALIS. *Warren M. Jacobs, M.D., F.A.C.S.*, Houston, Texas 233

EDITORIALS

THE "CURATIVE" RESECTION—A PREFERRED STATISTICAL UNIT FOR EVALUATING THERAPY IN CANCER OF THE STOMACH. *Stanley O. Hoerr, M.D., F.A.C.S.*, Cleveland, Ohio 237

AN AVERAGE SURGEON COMPLAINS. *Kenneth B. Castleton, M.D., F.A.C.S.*, Salt Lake City, Utah 239

THE SURGEON AT WORK

THE USE OF RAYON MESH IN SKIN GRAFTING AND GRANULATING WOUNDS. *Patrick C. Shea, Jr., M.D., F.A.C.S., William A. Reid, M.D.*, and *Albert H. Wilkinson, Jr., M.D.*, Atlanta, Georgia. 241

THE USE OF CONTINUOUS NEGATIVE PRESSURE AFTER LARYNGECTOMY AND RADICAL NECK DISSECTION. *F. Johnson Putney, M.D.*, Philadelphia, Pennsylvania 244

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS 247–252

BOOKS RECEIVED 252

AMERICAN COLLEGE OF SURGEONS

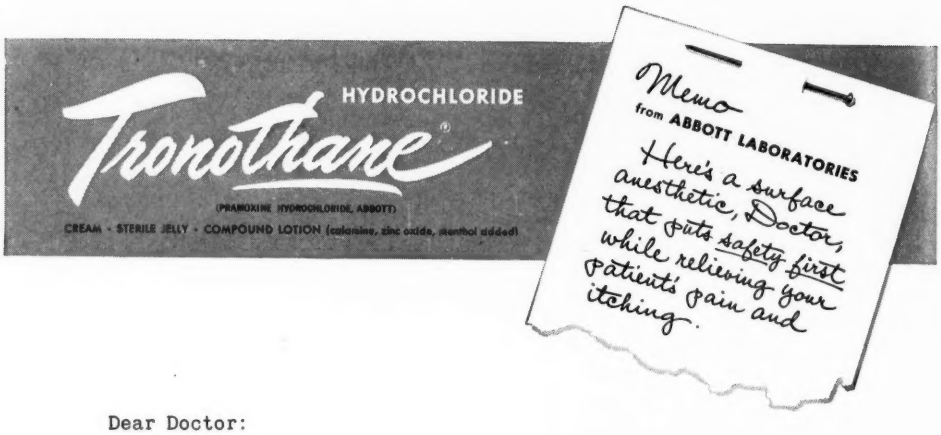
PRELIMINARY PLANS FOR THE 42ND CLINICAL CONGRESS, THE CIVIC AUDITORIUM, SAN FRANCISCO, CALIFORNIA, OCTOBER 8 TO OCTOBER 12, 1956 253

International Abstracts of Surgery

CONTENTS i-viii

COLLECTIVE REVIEW: STRANGULATION OBSTRUCTION; A CRITICAL REVIEW. *Isidore Cohn, Jr., M.D., F.A.C.S.*, New Orleans, Louisiana 105–137

ABSTRACTS OF IMPORTANT CONTRIBUTIONS IN THE CURRENT SURGICAL LITERATURE 138–208


HYDROCHLORIDE
Tronothane®
(PRAMOXINE HYDROCHLORIDE, ABBOTT)
CREAM · STERILE JELLY · COMPOUND LOTION (calamine, zinc oxide, menthol added)
Memo
from ABBOTT LABORATORIES
Here's a surface anesthetic, Doctor, that puts safety first while relieving your patients' pain and itching.

Dear Doctor:

A wide margin of safety is yours when you use Tronothane for surface anesthesia.

For with Tronothane, the incidence of sensitization is so low it is virtually insignificant. You can relieve pain or itching safely even in patients known to be sensitized to other topical agents.

To confirm this unusual freedom from side effects, clinical studies were made of Tronothane's use with more than 15,000 patients. These cases included anogenital pruritus, painful episiotomy, hemorrhoids, rectal surgery, and a wide variety of itching dermatoses, as well as burns and sunburn.

> Not one of these thousands evidenced toxicity. Primary sensitization was negligible. And cross-sensitization was not noted at any time.

Why is Tronothane so well tolerated? The answer is in the formula. Tronothane's chemical structure is in no way related to the agents derived from "caine" drugs. Para-aminobenzoic acids and benzoic acid are not included. Neither are certain chemical groups frequently associated with primary sensitization.

Put it to a test, Doctor, and see if this wide safety margin doesn't expand the usefulness of topical anesthesia in your daily practice.

Sincerely,

Abbott

SURGERY AUGUST 1956
Gynecology & Obstetrics VOLUME 103
NUMBER 2

THROMBOCYTOPENIA AND HEMORRHAGE IN HEMOLYTIC BLOOD TRANSFUSION REACTIONS

P. W. PIFER, M.D., M. A. BLOCK, M.D., and C. P. HODGKINSON, M.D., F.A.C.S.,
Detroit, Michigan

THAT AN ABNORMAL BLEEDING TENDENCY occurs with hemolytic blood transfusion reactions is well recognized. If a hemolytic blood transfusion reaction occurs at the time the patient is undergoing surgery, bleeding from the wound and all cut surfaces is almost uncontrollable. In an investigation of some of the coagulation factors during experimentally produced hemolytic blood transfusion reactions, we have observed a precipitous and marked fall in the platelet count in the circulating blood. Whether this reaction completely explains the bleeding tendency is uncertain, for changes in other factors do take place, such as a variable depression of plasma fibrinogen.

The period of critical decrease in platelets in the circulating blood does correlate with the abnormal bleeding tendency, and we have obtained additional evidence which also indicates that platelet count depression is a major cause of the abnormal bleeding tendency associated with hemolytic blood transfusion reactions.

From the Departments of Gynecology and Obstetrics and General Surgery, Henry Ford Hospital, Detroit.

METHODS

The experiments were performed by using adult dogs and rabbits with ether anesthesia for the dogs and intravenous sodium pentobarbiturate for the rabbits. Hemolysis was produced by the intravenous injection of fresh rabbit blood into the dogs. Usually the volume of rabbit blood administered approximated 15 per cent but varied from 10 to 30 per cent of the calculated blood volume of the dogs. The rapidity of injection of the rabbit blood was intentionally varied from 7 to 80 minutes, i. e., varying from a free flow to a slow drip. Eleven experiments were carried out. In addition, 4 similar experiments were performed in which dog blood was administered intravenously to rabbits. In 4 control experiments platelet and fibrinogen determinations were made on 2 rabbits and 2 dogs under anesthesia; no significant change occurred under anesthesia. In 1 experiment, homologous blood was administered intravenously to a dog with no significant change in platelet count or fibrinogen level.

Blood specimens were obtained by 1 investigator in order to insure uniformity in

TABLE I.—BLOOD COAGULATION FACTORS DURING AND AFTER COMPLETION OF INTRAVENOUS ADMINISTRATION OF HETEROLOGOUS BLOOD TO DOGS

Experiment No.	*Time after completion of infusion, mins.*	*Coagulation time, mins.*	*Bleeding time, mins.*	*Platelet count, per cu. mm.*	*Plasma fibrinogen, mgm. per cent*	*Blood hemoglobin, gm. per cent*	*Prothrombin time, per cent normal*
	Control	10	1	178,000	173	17.7	100
	10	No coagulation	—	18,000	142	—	100
	30	No coagulation	1¾	24,000	121	15.0	100
1.....	60	No coagulation	Indefinitely prolonged	27,000	128	—	100
	90	12	Indefinitely prolonged	—	132	—	100
	120	7	Indefinitely prolonged	39,000	123	13.4	100
	150	—	—	66,000	133	—	100
	Control	6	1 5/12	224,000	207	14.2	100
	During infusion	5	9⅛	34,000	170	13.2	100
2.....	5	6	8 11/12	16,000	162	11.8	100
	30	7	—	46,000	140	12.4	100
	45	5	19	40,000	148	12.2	100
	70	4½	—	78,000	154	12.4	100
	Control	7	3¼	290,000	252		100
	30	18	32	4,000	238		100
3*.....	45	5	30	22,000	235		100
	75	6	35	90,000	248		100
	105	7	30	212,000	232		100
	125	7	—	194,000	229		100
	Control (After infusion started)	7	1	162,000	257		
	15	10	6	14,000	266		
	30	8½	30	20,000	244		
4.....	60 (After infusion completed)	9	8	30,000	253		
	10	9	7	42,000	241		
	40	8	12	40,000	224		
	70	6½	5	96,000	231		
	100	7	—	127,000	226		

*Received 100 milligrams of protamine sulfate during experiment.

obtaining and handling the specimens. Blood was removed directly by syringe and needle from exposed femoral vessels. After initial control blood specimens were taken, the transfusion was given. Immediately following completion of the transfusion, in most experiments, blood specimens were again taken and determinations repeated at frequent intervals for approximately 1 to 3 hours. In a few experiments, blood specimens were also taken during the transfusion. If the animal survived, blood specimens were also obtained on subsequent days. The following determinations were carried out: plasma fibrinogen by the Wu-Ling method (normal range 200 to 400 mgm. per cent), platelet count by the Rees-Ecker method, hemoglobin by the electrophotometer, coagulation time according to the Lee and White technique, and prothrombin time by the Quick procedure (19). Bleeding times, not entirely satisfactory in animals, were taken by the Duke method.

RESULTS

The most striking finding was the precipitous and marked decrease in blood platelet count (Fig. 1). The platelets decreased to a value as low as 1.4 per cent of the control value with the range varying from 1.4 to 36 per cent of control values in the various experiments. The platelets remained at a low level for a period of from 1 to 2 hours following completion of the transfusion and then gradually returned to preinfusion levels. Twenty-four hours later the values were within normal limits. Data from 4 typical experiments in which rabbit blood was administered intravenously to dogs are shown in Table I.

The animals all exhibited an abnormal bleeding tendency starting during the infusion of the heterologous blood and continuing for several hours after its completion. Blood oozed continuously from wounds and bleeding occurred from areas of trauma.

The bleeding times were prolonged in all dogs except 1 in which the platelet count fell to only 27.5 per cent of the control level. The coagulation time varied. In 6 of the 11 experiments in which rabbit blood was given to dogs there was a considerable prolongation of coagulation time, the blood taken at the time of maximum diminution of platelets never actually coagulating. No change in coagulation time was noted in the other 5 experiments on dogs. Bleeding and coagulation times usually returned to almost normal levels 2 to 3 hours after completion of the infusion.

Plasma fibrinogen levels were consistently reduced but the decrease was usually not excessive and never reached critical levels (Fig. 2). The prothrombin time remained normal throughout all experiments. Blood hemoglobin usually fell 1 to 2 grams following the infusion of heterologous blood. If the animals survived, all determinations were within normal limits 24 hours after completion of the infusion of heterologous blood.

Shortly after the onset of infusion of heterologous blood, the animals were observed to become hyperpneic with a rapid, weak pulse. These changes were more marked if the blood was given rapidly, and the animals nearly expired in several instances. In general, the depression of plasma fibrinogen seemed to be greater in experiments in which the infusion was rapid.

Gross hemolysis was evident in plasma and urine immediately after the heterologous blood was infused. Three of the dogs receiving heterologous blood died within 24 hours following the experiment, and 2 died several days later. The experiment was intentionally terminated 2 hours after completion of the infusion on 3 occasions. Three

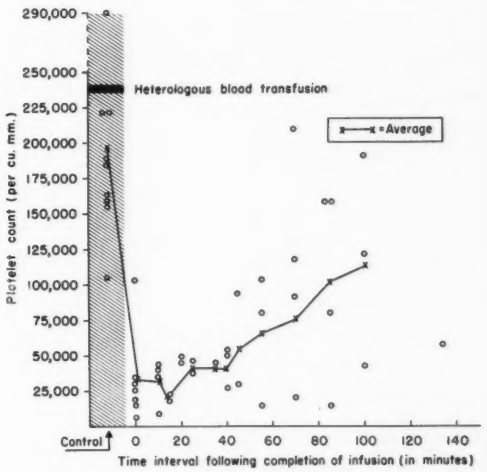


FIG. 1. Severe thrombocytopenia after intravenous administration of heterologous blood.

of the 4 rabbits receiving heterologous blood died within 24 hours after completion of the infusion. In the animals which failed to survive, hemorrhagic areas were noted in tissues scattered throughout the body, especially in the spleen and lungs. The kidneys showed the changes of hemoglobinuric nephrosis.

In 1 dog (Figs. 3 and 4) a transfusion of 400 cubic centimeters of homologous blood was given 12 days following the infusion of 300 cubic centimeters of heterologous blood. The changes in coagulation factors after the administration of heterologous blood were typical of those presented in the foregoing. No change in blood coagulation factors was observed as a result of the infusion of homologous blood. Then 24 days after the original heterologous blood infusion and 12 days after the homologous blood infusion, fresh heterologous blood was again administered. After the dog received 35 cubic centimeters of the blood, its condition became so serious that the infusion was terminated. The platelet count fell to low levels, and the blood failed to coagulate. The dog died within 12 hours.

In 2 of the experiments in which heterologous blood was administered to dogs, 100

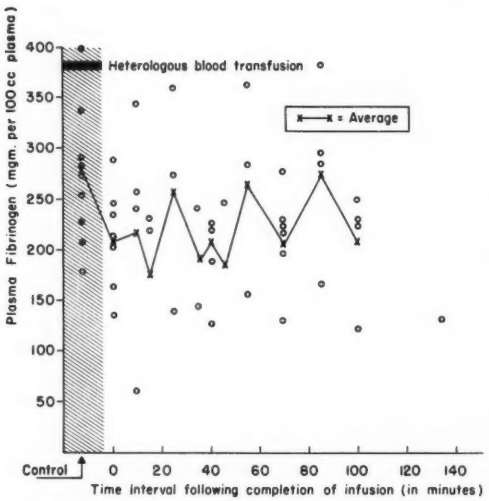


FIG. 2. Plasma fibrinogen after intravenous administration of heterologous blood.

milligrams of protamine sulfate were also given intravenously during the experiment. This was done in an effort to neutralize the effect of any heparin-like substance which might have been producing the bleeding tendency. However, both of these animals developed an abnormal bleeding tendency, their bleeding times were prolonged, and they showed the usual decrease in the platelet count without serious alteration in the other blood coagulation factors studied.

In 2 of the experiments, fresh blood from a normal dog was added in vitro to the blood having a prolonged coagulation time as a result of the administration of rabbit blood to the dog. Upon the addition of fresh normal blood, the nearly incoagulable blood clotted immediately. This reaction was interpreted as indicating that the blood failed to coagulate normally because of a deficiency of one of the coagulation factors and not as a result of the addition in vivo of an anticoagulant.

DISCUSSION

It appears that the bleeding tendency associated with the hemolytic blood transfusion reactions observed in man can be reduplicated experimentally. Nelson, Melnick, McKay, and their associates have also produced a hemorrhagic state experimentally by the infusion of incompatible blood or hemolyzed blood. It is not possible to be certain that the cause of the bleeding tendency in animals is the same as in man. It is also not possible to state whether one or multiple deficiencies in blood coagulation factors are responsible for the occurrence of the abnormal bleeding tendency. From our studies, incomplete in that not all blood coagulation factors were determined, it appears that the extreme reduction in platelets may be an important factor. A relatively minor reduction in plasma fibrinogen was also observed. The depression in the plasma fibrinogen level did not appear to be severe enough in itself to account for the abnormal bleeding tendency and may be a nonspecific effect of tissue injury as has been demonstrated by Hodgkinson and coworkers (8, 18).

It is well known that in anaphylactic and peptone shock a bleeding tendency takes place. A rise in blood heparin has been blamed for this occurrence by Jaques (10, 11, 23). A sudden release of histamine and a precipitous decrease in circulating platelets also are characteristic findings in anaphylactic and peptone shock according to Quick and associates (20). The intensity of these 3 findings is apparently unrelated.

Whether the sudden release of a heparin or heparin-like substance is the cause of the bleeding tendency in hemolytic transfusion reactions cannot be stated. There is some evidence of such an occurrence, however, and Muirhead has reported that the administration of toluidine blue arrests the bleeding tendency in some instances in humans. Jaques and Waters (10, 11) reported the isolation of heparin from the blood of dogs during anaphylaxis but were unable to detect it in normal dogs. They also presented evidence that the origin of the heparin was from the liver in the dog. However, they did observe that even in the hepatectomized dog, the clotting time was prolonged

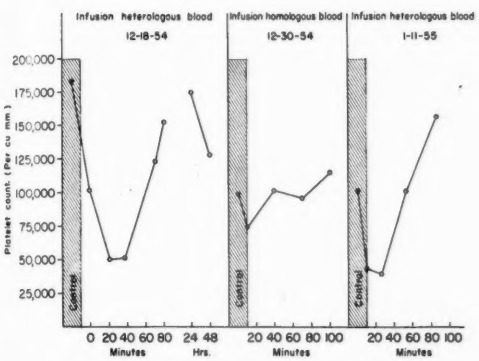


FIG. 3. Severe thrombocytopenia after heterologous blood transfusion; little change in platelet count after homologous blood transfusion.

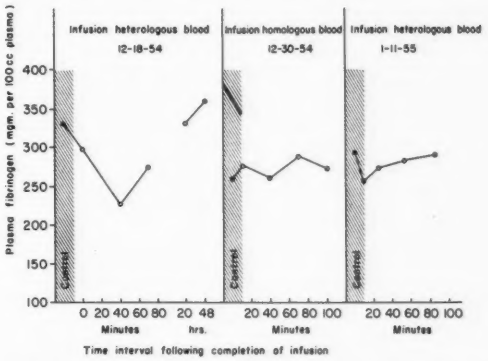


FIG. 4. Plasma fibrinogen levels (mgm. per 100 c.c. of plasma) after transfusions of heterologous and homologous blood.

but the amount of heparin required to return the clotting time to normal was low in these animals. They suggested that a diminution of platelets might have contributed to the prolongation of the clotting time. Schultz had already reported in 1925 that the addition of platelets to incoagulable blood of animals in anaphylaxis produced coagulation in a few minutes. Our observations confirm those of Schultz with respect to incoagulable blood following hemolytic blood transfusion reactions and suggest that platelet depression rather than a heparinoid anticoagulant is responsible for the bleeding tendency.

In our experiments on hemolytic blood transfusion reactions, the bleeding tendency occurred in spite of normal coagulation times and the administration of protamine sulfate. The only consistently marked finding in our studies was the diminution of platelets. Incoagulable blood produced in our experiments clotted upon the addition of fresh homologous blood. The data suggest that the thrombocytopenia has a leading role in causing the bleeding tendency. Yet, we do not believe the evidence is positive proof that the thrombocytopenia is the only or even the major cause of the bleeding tendency associated with hemolytic transfusion reactions. Actually, the bleeding tendency may be well due to alterations in a number of coagulation factors, for we did observe a decrease in both plasma fibrinogen and platelet values.

The cause of the thrombocytopenia observed in hemolytic transfusion reactions also is a problem to be considered. The decrease in platelets may well be due to their adhering to each other forming clumps of varying sizes. This observation was made by Quick, Ota, and Baronofsky (20) and by Eagle, Johnston, and Ravdin in anaphylactic and peptone shock. The clumps of platelets may then be removed from the circulation by the capillary bed. The agent or factor responsible for the platelet agglutination is unknown. Quick, Ota, and Baronofsky found that the intravenous injection of large doses of heparin does not prevent the platelet agglutination. It is possible that platelet agglutinins could be present to produce the platelet agglutination but Evans and co-authors report that platelet agglutinins probably occur in only a small percentage of humans. McKay and co-workers (6, 14) report the findings of disseminated platelet and fibrin thrombi following incompatible blood transfusions in dogs, especially if the blood is injected rapidly.

In our experiments the coagulation time was prolonged in approximately one-half of the animals only, but the prolongation was definite in those animals. Prolongation of bleeding time was a rather consistent finding. These variations might be interpreted

as indicating that multiple factors are involved in the clinically evident bleeding tendency. It is known that significant thrombocytopenia will cause a prolongation of the bleeding time but the coagulation time is lengthened only by an almost total removal of the platelets. This fact could account for the variations in the coagulation time observed. The coagulation time depends on several factors while the platelets seem to be the predominant factor in the bleeding time determination.

It appears that the mechanisms underlying the coagulation defect in incompatible blood transfusions have certain similarities, yet distinct differences from those which are the basis of the bleeding tendency which sometimes occur in certain obstetric conditions, i. e., abruptio placentae, amniotic fluid embolism, and prolonged intrauterine retention of a dead fetus. In the experimentally produced incompatible blood transfusions, platelet agglutination or thrombus formation in the smaller blood vessels appears to occur primarily with the bleeding tendency largely related to the resultant thrombocytopenia. In the obstetric conditions, fibrin emboli and thrombus formation appear experimentally to occur primarily with the bleeding tendency related largely to the resultant hypofibrinogenemia. Platelets are also decreased but have not been consistently studied. However, in both hemolytic blood transfusion reactions and the obstetric conditions, thrombus formation does not appear to be purely of one type, so that both fibrin and platelet thrombi are found, and a reduction in a number of coagulation factors occurs in both conditions with considerable variations in individual animal experiments or patients.

Crosby and Stefanini also emphasize that a nonspecific pattern of changes occurs during anaphylactic and peptone shock, incompatible transfusions, the intravenous administration of foreign proteins, and what they describe as the plasma transfusion reaction which occurs in patients with hemolytic disease. In these conditions, emboli composed of platelets and fibrin form and lodge in small vessels over the body. Thrombocytopenia and hypofibrinogenemia result with a diminution in other coagulation factors manifested by a bleeding tendency.

Recently, Artz and Howland and their co-workers have called attention to the bleeding tendency which is associated with massive blood replacement. The etiology of the bleeding tendency in this situation also is not definite. Several factors may be involved. Krevans and Jackson have emphasized thrombocytopenia as an important abnormality underlying this hemorrhagic state.

The severe bleeding tendency associated with hemolytic transfusion reactions occurring during surgery is a serious and life endangering condition. Muirhead observed that the hemorrhagic state seemed to occur after larger volumes of incompatible blood were given. Since the underlying abnormalities are incompletely understood in man, the treatment is not established. Transfusion of fresh compatible blood should be of value. Since Hardaway, McKay, and Williams (7) reported a critical hypofibrinogenemia in a human with hemorrhage associated with an incompatible blood transfusion and since hypofibrinogenemia may be a more critical factor in man as a species variation in this condition, the administration of fibrinogen may be of real value.

SUMMARY AND CONCLUSIONS

1. The intravenous administration of heterologous blood experimentally results in an abnormal bleeding tendency similar to that observed in hemolytic blood transfusion reactions in man.

2. A critical precipitous fall of blood platelets is associated with the hemolytic transfusion reaction. A small decrease in plasma fibrinogen also occurs. The bleeding time is usually prolonged and frequently the coagulation time is prolonged. These changes usually are only of several hours duration.

3. The intravenous administration of protamine sulfate did not significantly influence the abnormalities observed.

4. The platelet depression appears to be of major importance in the etiology of the bleeding tendency observed experimentally. Whether platelet depression is the primary reason for the bleeding tendency associated with incompatible blood transfusions in man is unknown.

5. It appears that fibrin and platelet emboli or thrombi form in blood vessels throughout the body as a nonspecific reaction occurring in a number of conditions in which foreign proteins are present in the blood stream. This condition then results in thrombocytopenia and hypofibrinogenemia and a bleeding tendency. In varying situations either thrombocytopenia or hypofibrinogenemia may predominate.

REFERENCES

1. Artz, C. P., Sako, Y., and Bronwell, A. W. Massive transfusion in the severely wounded. Surgery, 1955, 37: 469–472.
2. Crosby, W. H., and Stefanini, M. Pathogenesis of the plasma transfusion reaction with especial reference to the blood coagulation system. J. Laborat. Clin. M., 1952, 40: 374–386.
3. Duke, W. W. The relation of blood platelets to hemorrhagic disease; description of a method for determining the bleeding time and coagulation time and report of three cases of hemorrhagic disease relieved by transfusion. J. Am. M. Ass., 1910, 55: 1185–1192.
4. Eagle, H., Johnston, C. G., and Ravdin, I. S. On the prolonged coagulation time subsequent to anaphylactic shock. Bull. Johns Hopkins Hosp., 1937, 60: 428–438.
5. Evans, R. S., Takahashi, K., Duane, R. T., Payne, R., and Liu, C. K. Primary thrombocytopenic purpura and acquired hemolytic anemia; evidence for a common etiology. Arch. Int. M., 1951, 87: 48–65.
6. Hardaway, R. M., McKay, D. G., Wahle, G. H., Jr., Tartock, D. E., and Edelstein, R. Pathologic study of intravascular coagulation following incompatible blood transfusion in dogs—I, intravenous injection of incompatible blood. Am. J. Surg., 1956, 91: 24–31.
7. Hardaway, R. M., McKay, D. G., and Williams, J. H. Lower nephron nephrosis (ischemuric nephrosis) with special reference to hemorrhagic diathesis following incompatible blood transfusion reaction. Am. J. Surg., 1954, 87: 41–49.
8. Hodgkinson, C. P., Pifer, P. W., and Remp, D. G. Plasma fibrinogen and surgical trauma. Henry Ford Hosp. M. Bull., 1954, 2: 44–55.
9. Howland, W. S., Schweizer, O., Boyan, C. P., and Dotto, A. C. Physiologic alterations with massive blood replacement. Surg. Gyn. Obst., 1955, 101: 478–482.
10. Jaques, C. B., and Waters, E. T. The isolation of a crystalline heparin from the blood of dogs in anaphylactic shock. Am. J. Physiol., 1940, 129: 389–390.
11. Idem. The identity and origin of the anticoagulant of anaphylactic shock in the dog. J. Physiol., 1941, 99: 454–466.
12. Krevans, J. R., and Jackson, D. P. Hemorrhagic disorder following massive whole blood transfusion. J. Am. M. Ass., 1955, 159: 171–177.
13. Lee, R. I., and White, P. D. A clinical study of the coagulation time of blood. Am. J. M. Sc., 1913, 145: 495–503.
14. McKay, D. G., Hardaway, R. M., Wahle, G. H., Jr., Edelstein, R., and Tartock, D. E. Alteration in the blood coagulation mechanism following incompatible blood transfusion; clinical and experimental observations. Am. J. Surg., 1955, 89: 583–592.
15. Melnick, D., Burack, E., and Cowgill, G. R. Development of incompatibilities in dogs by repeated infusion of red blood cells. Proc. Soc. Exp. Biol., N.Y., 1937, 33: 616–621.
16. Muirhead, E. E. Incompatible blood transfusions with emphasis on acute renal failure. Surg. Gyn. Obst., 1951, 92: 734–746.
17. Nelson, R. M., Eder, W. P., Eddy, F. D., Karlson, E. E., and Denis, C. Production of a hemorrhagic state by the infusion of hemolyzed blood. Proc. Soc. Exp. Biol., N.Y., 1950, 73: 208–209.
18. Pifer, P. W., Block, M., and Hodgkinson, C. P. Experimental hypofibrinogenemia. Henry Ford Hosp. M. Bull., 1955, 3: 112–118.
19. Quick, A. J. Nature of bleeding in jaundice. J. Am. M. Ass., 1938, 110:1658–1662.
20. Quick, A. J., Ota, R. K., and Baronofsky, I. D. On the thrombopenia of anaphylactic and peptone shock. Am. J. Physiol., 1946, 145: 273–278.
21. Rees, H. M., and Ecker, E. E. Improved method for counting blood platelets. J. Am. M. Ass., 1923, 80: 621–622.
22. Schultz, E. W. Platelet deficiency; a factor in diminished coagulability of the blood in anaphylaxis. Proc. Soc. Exp. Biol., N.Y., 1925, 22: 343–344.
23. Waters, E. T., Markowitz, J., and Jaques, C. B. Anaphylaxis in the liverless dog, and observations on the anticoagulant of anaphylactic shock. Science, 1938, 87: 582–583.
24. Wu, H., and Ling, S. M. Colorimetric determination of proteins in plasma, cerebrospinal fluid and urine. Chin. J. Physiol., 1927, 1: 161–168.

THE TREATMENT OF SELECTED CASES OF MULTIPLE POLYPS, FAMILIAL POLYPOSIS, AND DIVERTICULAR DISEASE OF THE COLON BY SUBTOTAL COLECTOMY AND ILEOPROCTOSTOMY

IRA TEICHER, M.D., F.A.C.S., and JESSE I. ABRAHAMS, M.D., Brooklyn, New York

SUBTOTAL COLECTOMY and ileoproctostomy have been accepted as a definitive procedure for a variety of lesions of the colon. The operation is extensive and most surgeons have reserved it for the resection of multiple malignant lesions of the colon or for the treatment of suitable cases of polyposis. In spite of the extent of the procedure, the mortality rate can be kept low if patients are properly prepared and are given adequate support during and after operation. It has been observed that if the ileoproctostomy is carried out with preservation of the terminal ileum and only a few inches of terminal rectum, these patients show little if any abnormality in bowel function. The fact that the operation can be performed with a low mortality and that it does not leave the patient with any disturbing functional or nutritional deficit has prompted the wider application of the procedure. The present report deals with the results obtained by this operation in 5 patients with multiple colonic polyps, 2 with familial polyposis of the colon, and 1 with diverticulosis of the colon with repeated hemorrhage. Seven of these selected patients have been carefully followed at frequent intervals in order to record bowel function and visualize the anastomosis and distal segments.

MULTIPLE POLYPS

The diagnosis and management of multiple polyps of the colon present a challenge to the radiologist and the surgeon. Authorities are firm in their conviction that most adenocarcinomas of the colon arise from pre-existing polyps. Accordingly, the diagnosis and eradication of these polyps can provide an important form of prophylaxis against cancer. Fortunately, about two-thirds of the polyps are in the rectum and lower sigmoid, within reach of the 25 centimeter sigmoidoscope. However, in approximately 35 per cent of the cases, multiple polyps are present, and accurate diagnosis of all the lesions is often difficult. Visualization of a polyp in the terminal colon or rectum is routinely followed by careful x-ray study of the proximal colon to detect additional polyps. As will be demonstrated in our case reports, many polyps, especially small ones, escape detection by x-ray examination. The deficiency of this method of diagnosis was emphasized by Deddish and Hertz in their report of 103 patients who underwent colotomy and coloscopy for polypoid disease of the colon. At operation they found that 46.6 per cent of the patients had more polyps than were detected by at least 2 preoperative barium enemas. This fact casts great doubt on the accuracy of frequently quoted statistics concerning the occurrence and recurrence of polyps. The true figures are apparently higher.

The following case reports describe the management of 5 patients with multiple polyps of the colon.

From the Surgical Service of the Veterans Administration Hospital and the University Surgical Service of Kings County Hospital, Brooklyn, New York, and the State University of New York, College of Medicine at New York City.

CASE 1. M. O., a 56 year old white male, was admitted to the Brooklyn Veterans Administration Hospital on August 22, 1952 because of abdominal pain

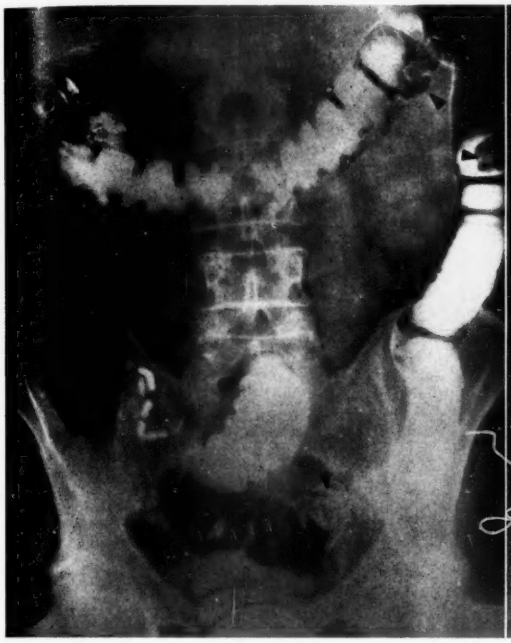


FIG. 1.

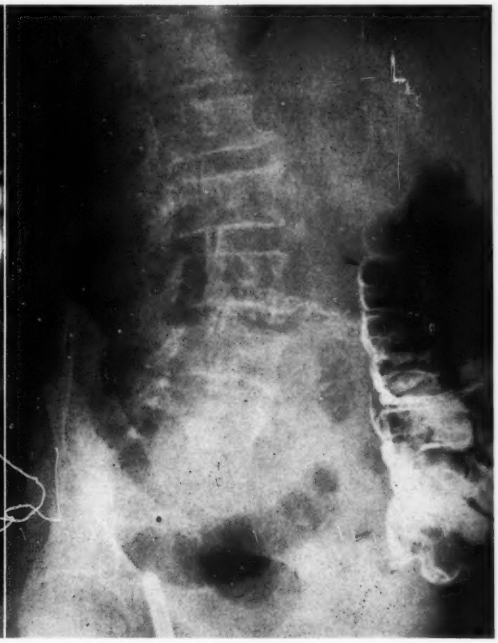


FIG. 2.

FIG. 1. Case 1. Barium enema with air contrast study demonstrating 3 polyps in the left colon. Two polyps in right colon not visualized.

FIG. 2. Case 2. Barium enema with air contrast study demonstrating 2 polyps. Ten polyps not seen.

and passage of tarry stool. X-ray series of the upper gastrointestinal tract were reported as negative, and a barium enema with air contrast study revealed 3 polypoid defects (Fig. 1). These were located in the distal transverse, mid-descending, and sigmoid colon. Sigmoidoscopy was negative for 20 centimeters. On October 3, 1952 an exploratory operation was performed, and palpation not only confirmed the presence of the 3 polyps noted on barium enema but also revealed a polyp in the hepatic flexure and 1 in the cecum. Exploration of the remainder of the abdomen demonstrated a chronic duodenal ulcer. Colotomy was not performed and subtotal colectomy with end-to-end ileoproctostomy was carried out because of the presence of multiple polyps. Examination of the operative specimen revealed a .5 centimeter sessile polyp in the sigmoid, in addition to the 3 polyps noted on the x-ray film and the additional 2 discovered at surgery. The palpable polyps varied from 1 to 2 centimeters in diameter. Microscopic examination revealed atypism in one and noninvasive malignancy in another.

The postoperative course was entirely uneventful, and at the time of discharge from the hospital, the patient was having 2 to 3 formed stools a day. This bowel function has persisted and he is asymptomatic on an ulcer diet. Sigmoidoscopic examination revealed the anastomosis to be 15 centimeters from the anal verge and no additional polyps have been noted in the rectum.

CASE 2. R. K., a 76 year old white male, was investigated at the Brooklyn Veterans Administration Hospital because of rectal bleeding. On February 2, 1953 three sessile polyps found in the rectum were excised and the bases fulgurated via sigmoidoscopy. These were noted at 10, 15, and 22.5 centimeters from the anal verge, and the microscopic report was adenomatous polyps. He was readmitted to the hospital on September 15, 1953 because a barium enema demonstrated a polypoid filling defect in the transverse colon and a similar defect in the proximal descending colon (Fig. 2).

On October 13, 1953 exploration was carried out and the descending colon polyp was excised via colotomy. Coloscopy revealed an additional polyp in the descending colon and this was also excised. A second colotomy was made at the site of the palpable transverse colon polyp and this lesion was removed. Coloscopy was then performed through this incision and polyps of the ascending colon were noted. The examination of the entire ascending colon was not satisfactory, and because of diffusely scattered polyps,

subtotal colectomy was carried out. Examination of the surgical specimen revealed 9 polyps in addition to the 3 excised. Five of these were found in the ascending colon and hepatic flexure, 2 in the splenic flexure, and 2 in the sigmoid. These measured up to 2.5 centimeters in diameter. All 12 were reported as benign adenomatous polyps.

The postoperative course was uneventful and since discharge the patient has been having 1 to 2 formed stools a day. The anastomosis is visualized 16 centimeters from the anus, and the rectum is completely normal.

CASE 3. J. T., a 71 year old white male, was admitted to Kings County Hospital on September 14, 1954 because of diarrhea and melena. Sigmoidoscopy revealed 3 pedunculated polyps and 1 sessile polyp to be present at a level between 13 and 17 centimeters from the anus. These were excised and found to be benign polyps. Barium enema and air contrast studies failed to demonstrate any additional disease. It was deemed advisable that the patient have a subtotal colectomy because of the likelihood of other polyps in his colon.

Operation was performed on November 1, 1954 and no lesions were palpated in the colon. A subtotal colectomy was carried out anastomosing terminal ileum to the rectosigmoid. Examination of the excised specimen revealed the presence of 5 sessile polyps. Two were in the ascending colon, 1 in the hepatic flexure, and 2 in the sigmoid. All polyps were benign.

Since discharge from the hospital the patient has been asymptomatic, has maintained a normal weight, and has 1 to 2 formed stools daily. The anastomosis is visualized at a level of 13 centimeters from the anal verge. On March 17, 1955, he was readmitted because of a fractured hip. Internal fixation was carried out and he tolerated the operative procedure without difficulty.

These 3 cases demonstrate the relative inaccuracy of x-ray examination in the diagnosis of polyps of the colon. Despite repeated studies with air contrast techniques, numerous polyps escaped detection in each case. The uncertainties usually encountered in the surgical management of these patients were eliminated by performing subtotal colectomies.

In the next 2 case reports, patients are described who were subjected to multiple operative procedures. This type of management can be contrasted with the initial treatment by subtotal colectomy.

CASE 4. B. S., a 70 year old white male, was admitted to Kings County Hospital on March 14, 1954 because of diarrhea and melena. He had a history of drinking excessive amounts of wine and whiskey for many years. Sigmoidoscopy for 25 centimeters was negative except for the presence of tarry stools, and barium enema demonstrated a polypoid defect in the mid-ascending colon (Fig. 3).

An exploratory operation was performed on March 18, 1954 and a fleshy mass was palpated in the ascending colon. Clinical impression of cancer was entertained and a right hemicolectomy with aseptic end-to-end ileotransverse colostomy was performed. Subsequent examination of the surgical specimen revealed the presence of about 50 polyps distributed from the cecum to within 5 centimeters of the distal line of resection. These varied from 0.5 to 3 centimeters in diameter. In the ascending colon a 3 centimeter polyp with an indurated base was found to have invasive adenocarcinoma extending to the serosa. The remainder of the polyps were benign and lymph nodes were free of tumor. The patient was again explored on April 20, 1954 because of x-ray evidence of a polyp in the lower descending colon. The lesion was removed through a colotomy, and coloscopy was carried out. Two additional polyps were located in the proximal descending colon and excised through a second colotomy. Microscopic examination demonstrated polyps with foci of atypical hyperplasia. The patient was discharged to the clinic and subsequent x-ray and sigmoidoscopic examinations were negative. However, members of the tumor board believed that the residual left colon probably contained polyps, and recommended resection. On September 17, 1954 the procedure was carried out and ileum anastomosed to the rectosigmoid 12.5 centimeters from the anus. Examination of the resected specimen revealed 3 small benign polyps in the distal transverse colon. Since discharge the patient has been having 5 to 6 stools a day which are soft and intermittently liquid. Normal weight is maintained. Dietary management of the patient is difficult and he continues to drink large quantities of alcohol.

This patient could have been treated more aggressively at the time of his first operation. If the excised specimen was immediately examined by both surgeon and pathologist the presence of multiple polyps extending to within 5 centimeters of the distal line of resection would have suggested that additional polyps were present in the remaining colon. A frozen section of the firm polyp in the ascending colon might have demonstrated malignancy. Either of these observations would have provided ample indication to extend the resection to the rectosigmoid.

This patient is the only one in the group who has intermittent watery stools. A total

FIG. 3.

FIG. 4.

FIG. 3. Case 4. Polypoid defect in ascending colon demonstrated by barium enema. This defect was due to a cluster of large polyps. Many other polyps in colon not visualized.

FIG. 4. Case 5. Two adjacent filling defects in lower sigmoid seen on postevacuation study after barium enema. This lesion was a bilobed polyp. Numerous smaller polyps cannot be seen.

of only 15 centimeters of terminal ileum was resected and this should not be significant. The patient's continued intake of alcohol and his failure to conform to recommended dietary restrictions may be factors producing the diarrhea.

CASE 5. D. B., a 70 year old white male, was admitted to Kings County Hospital on July 25, 1955 with a 2 year history of red blood in his stools. Sigmoidoscopy revealed a 1.5 centimeter pedunculated polyp at a level of 17.5 centimeters and a 7 millimeter sessile polyp at a slightly higher level. These were excised and diagnosed as benign polyps with atypism of cells. After 2 negative barium enemas, a third study demonstrated 2 filling defects in the lower sigmoid (Fig. 4). On August 25, 1955 laparotomy was performed and palpation of the entire colon revealed only a polypoid mass in the lower sigmoid. This mass was inspected through a colotomy and found to be a bilobed 2 centimeter polyp. It was excised, and coloscopy of the left colon was carried out. No more polyps were seen, but the bowel was poorly prepared and visualization was unsatisfactory. Subsequent examination of permanent sections of the excised polyp revealed the presence of adenocarcinoma with invasion through the muscularis mucosa. This diagnosis made reoperation necessary. In view of the fact that 3 polyps had already been found and others were likely to be present, subtotal colectomy and ileoproctostomy was selected as the procedure of choice. The operation was performed on September 12, 1955. Examination of the resected colon revealed the presence of at least 50 polyps measuring up to 1 centimeter in diameter. A few were pedunculated but most were sessile. They were distributed along the entire colon down to within 5 centimeters of the distal resected margin. Microscopic examination demonstrated multiple benign polyps.

On the fourteenth postoperative day the patient had a mild cerebrovascular accident and thereafter remained lethargic. He had 1 to 2 formed stools daily but never informed the nurse of a desire to defecate, and accordingly was considered incontinent. A week later the patient had a second seizure and rapidly deteriorated. He expired on October 11, 1955, the twenty-ninth postoperative day. Autopsy was denied.

The patient's definitive treatment, after the diagnosis of invasive malignant disease

was established, was the subject of extensive staff discussions. We believed that more polyps were present in the colon even though they were not demonstrated by x-ray examination or operative sigmoidoscopy. The diagnosis of adenocarcinoma was an indication for left colectomy, but it was agreed that subtotal colectomy was a more desirable operation. This point was borne out by subsequent examination of the resected specimen. The numerous polyps were too small to be palpated or demonstrated by x-ray examination and were completely missed on coloscopy of the left colon.

If the polyp removed by colotomy at the first operation had been immediately examined, a diagnosis of malignant disease might have been made and definitive surgery carried out. In many cases a diagnosis of malignancy can be established on frozen section and the patient spared a second operative procedure. This patient constituted the only operative mortality in the reported series. His cerebrovascular complications made it difficult to evaluate the postoperative bowel function. Stools became solid and he developed good sphincter tone. However, after the second postoperative week the patient remained confused and was not considered to have demonstrated complete continence prior to exitus.

Discussion. If a polyp is demonstrated in the colon, laparotomy is indicated. The object of the operation is to remove the polyp visualized by x-ray examination, and to search for additional polyps that may be present in any other part of the colon. Palpation of the colon is useful in locating larger lesions but may be of no assistance in detecting small soft polyps. Coloscopy of the entire colon can be carried out through multiple colotomies and detected polyps removed via colotomy or by segmental resection. This operation under ideal conditions may result in eliminating all colonic polyps. However, one must be cognizant of the limitations of the procedure and the possibility of overlooking a variable amount of disease of the colon. Endoscopy can be unsatisfactory, and access to all segments of the colon may be difficult, especially in obese patients with short mesenteries and in patients with intestinal adhesions from previous operative procedures. Direct visualization of the entire mucosal surface of the colon may not be accomplished and polyps can be hidden in folds and obscured by fecal particles. One must also consider the problem encountered during operation of obtaining an accurate diagnosis of polyps excised via colotomy. Gross examination may not reveal which are benign and which are malignant, and immediate frozen section reports often cannot provide the answer. Subsequent fixed tissue sections may demonstrate invasive adenocarcinoma and the patient must be subjected to a second procedure for adequate surgery.

The management of a case of multiple polyps of the colon should include recognition of the fact that the patient has a colonic mucosa which is predisposed to form more polyps, and eventually carcinoma. Judd and Carlisle reported a follow-up study on 246 patients who had undergone a transcolonic excision of polyps at the Mayo Clinic. Twenty-eight per cent of the entire group developed additional polyps that required a second operation. However, these patients were not subjected to coloscopy, and some of the new lesions may have been old ones previously undetected. Similar findings were reported by Rider and his associates who had also noted that carcinoma of the colon and rectum occurred with 5 times greater frequency in "polyp patients" than in normal individuals. They reported that patients with multiple polyps were twice as likely to develop new polyps or carcinoma as were individuals with a single polyp. These studies indicate a relationship between the number of polyps and the carcinogenic potential of the colonic and rectal mucosa.

All of these facts make the treatment of multiple colonic polyps by colotomy, coloscopy, and even segmental resection a most disturbing procedure. If our objective is cancer prophylaxis, it cannot be achieved

by utilizing an operation which may not accomplish eradication of all polyps. Subtotal colectomy offers a solution to the problem of the total management of patients with multiple polyps of the colon. We do not believe that the risk of subtotal colectomy, in selected cases, is much greater than the total risk of those lesser procedures which may leave the patient with residual polyps.

It is difficult to set up rigid criteria for the selection of subtotal colectomy as the operation of choice. Every patient must be individually evaluated. We suggest that if a preoperative diagnosis establishes the presence of 3 or more polyps in different parts of the colon, subtotal resection is advisable. We also suggest that if 2 or more polyps are found and examination of any one reveals adenocarcinoma to be present, subtotal colectomy should be carried out. The demonstration of clusters of polyps in any single area of the colon indicates that other polyps are likely to be present, and subtotal colectomy appears justified. During the course of a colotomy undertaken because of the diagnosis of a solitary polyp, palpation of the colon or operative endoscopy may reveal the presence of multiple polyps. Such a patient would, in our opinion, be served best by subtotal colectomy. In the 5 cases with multiple polyps reported in this article, there were varying indications for subtotal colectomy and we believed that it proved to be the most desirable procedure. All carcinogenic foci were removed and the patients had minimal postoperative bowel dysfunction.

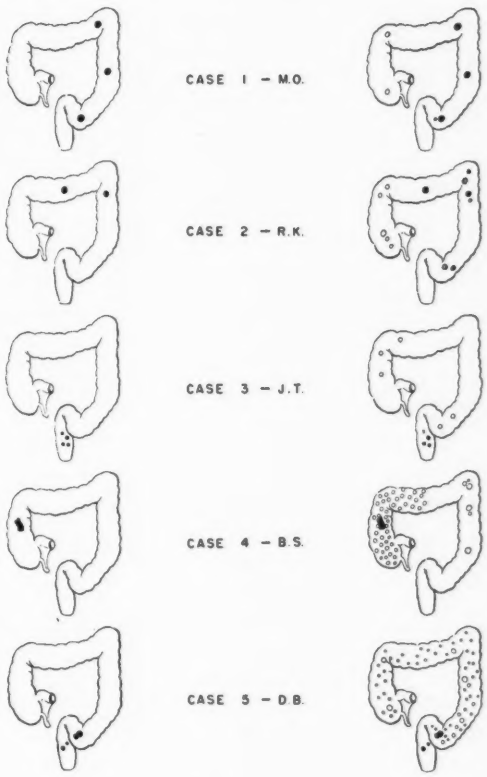


FIG. 5. Drawing demonstrating the discrepancy between, a, the preoperative diagnosis—polyps found by preoperative roentgenograms and sigmoidoscopy—and, b, postoperative findings—number of polyps found after colectomy—in 5 cases of multiple polyps of the colon.

CARCINOMA OF THE COLON

A discussion of the application of subtotal colectomy for carcinoma of the colon is beyond the scope of this paper. However, the radical procedure is being more widely utilized because of the frequent occurrence of polyps associated with a neoplasm, and the 5 per cent incidence of multiple colonic cancers. Mayo and Schlicke, in 1942, demonstrated these facts in a report of 131 necropsies performed on patients who died within 3 weeks following resection for carcinoma of the colon and rectum. They found that 37.4 per cent had polyps in the remaining colon and a second carcinoma was present in the residual colon in 5.3 per cent of cases. These are the facts that are influencing many surgeons who now declare that the conventional hemicolectomy is inadequate. Removal of half of the colon is aimed at excision of the lymphatic pathways of spread but neglects the local factors in the residual colon. Polyps and a second neoplasm may be left behind. Some surgeons are now collecting statistics on the utilization of subtotal colectomy for all carcinomas of the colon. Others are adopting a more conservative approach

TABLE I.—BOWEL FUNCTION AFTER SUBTOTAL COLECTOMY AND ILEOPROCTOSTOMY

Case No. Patient	*Length of rectal segment, cm.*	*Length resected ileum, cm.*	*No. of daily stools*	*Consistency of stools*	*Weight since operation*	*Control*	*Cramps*	*Urgency to defecate*	*Passage of flatus*
1 M.O.	15	15	2 to 3	Formed	Stable	Continent	None	None	Less
2 R.K.	16	5	1 to 2	Formed	Gained	Continent	None	None	Increased
3 J.T.	13	5	1 to 2	Formed	Stable	Continent	None	None	Same
4 B.S.	12.5	15	5 to 6	Watery or semisolid	Stable	Continent	Frequent	Occ.	Same
5 D.B.*	15	3	1 to 2	Formed		Incontinent			
6 I.L.O.	12.5	3	1 to 2	Formed	Slight loss	Continent	None	None	Increased
7 G.B.	12.5	11	2 to 3	Semisolid or formed	Gained	Continent	None	None	Less
8 N.F.	15	8	2 to 3	Semisolid or formed	Stable	Continent	None	None	Increased

*Patient expired on 29th postoperative day.

and regulate the extent of resection on the operative findings. After a hemicolon containing a carcinoma is removed, it is immediately opened and examined. The residual colon is then visualized by coloscopy. The presence of polyps in either the surgical specimen or the residual colon is accepted as an indication to extend the resection to a subtotal colectomy.

FAMILIAL POLYPOSIS

Two cases of familial polyposis are presented primarily to describe function of the bowel after subtotal colectomy.

Case 6. I. L. O., a 27 year old white male, was admitted to the Manhattan Beach Veterans Administration Hospital in January of 1949 after 4 months of rectal bleeding. A family history revealed that his mother and 1 maternal aunt had died from cancer of the colon. By sigmoidoscopic examination numerous polyps were visualized in the rectum and rectosigmoid. Barium enema with air contrast studies revealed polyps throughout the entire colon (Fig. 6). A diagnosis of familial polyposis was made and total colectomy was advised, but the patient refused to have an ileostomy. Accordingly, after preliminary fulguration of all rectal polyps, a two stage subtotal colectomy and ileoproctostomy was carried out. The resected colon contained numerous benign polyps measuring 3 millimeters to 1.5 centimeters as well as a few larger polyps. The patient has enjoyed completely normal bowel function following the subtotal colectomy. He has 1 to 2 solid stools daily, eats well, and maintains his weight. A proctoscopic examination is made every 3 months and the anastomosis is visualized 12.5 centimeters from the anal verge. Several new polyps have appeared in the rectal segment since colectomy and they have been excised and the bases fulgurated. Examination revealed all to be benign adenomatous polyps.

Case 7. G. B., a 41 year old white male, was admitted to the Brooklyn Veterans Administration Hospital on September 6, 1952 with acute abdominal pain. He was subsequently operated on for drainage of an abscess of the body of the pancreas. After recovery, sigmoidoscopy was performed and innumerable polyps, measuring from 5 millimeters to 2 centimeters were noted in the rectum and rectosigmoid. A barium enema with air contrast study was performed and countless polyps were seen throughout the colon (Fig. 7). Family history revealed that his father and 2 brothers had had cancer of the colon. A diagnosis of familial polyposis was made and total colectomy advised. The patient refused to have an ileostomy but was amenable to subtotal resectional surgery. Fulguration of the polyps in the rectum was then carried out and numerous specimens were taken for biopsy. All were benign except for 1 polyp at 22.5 centimeters which showed noninvasive malignancy. On April 27, 1953 a subtotal colectomy with end-to-end ileoproctostomy was performed with the anastomosis at 12.5 centimeters from the anus. Examination of the surgical specimen revealed hundreds of polyps, raised, flat, and sessile, varying from 3 millimeters to 1.5 centimeters in diameter. One of these larger polyps had mitotic figures and invasion of the muscularis mucosa, diagnosed as adenocarcinoma. No other malignant disease was noted, but many adenomatous polyps had atypism of cells.

Following discharge from the hospital the patient underwent fulguration of approximately 15 residual rectal polyps. Thereafter, proctoscopic examinations

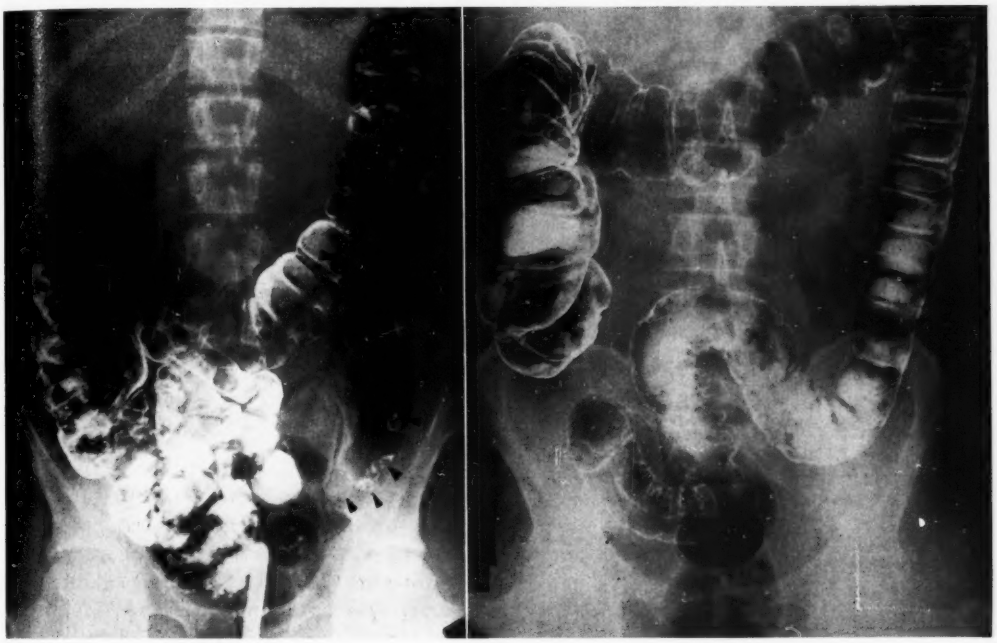


FIG. 6. FIG. 7.

FIG. 6. Case 6. Barium enema with air contrast study showing many large polyps but failing to visualize diffusely distributed small polyps.

FIG. 7. Case 7. Numerous polyps distributed throughout the entire colon demonstrated by air contrast roentgenograms.

have been carried out every 3 months and the rectal segment continues to be free of polyps. The patient is completely asymptomatic and has 2 to 3 formed stools per day with normal control.

These 2 patients with familial polyposis both refused ileostomy in favor of ileoproctostomy. They are included in this study to demonstrate that choice of the latter procedure afforded them essentially normal bowel function. Both are intelligent and realize the necessity of continued follow-up at 3 month intervals for the rest of their lives. The danger of malignant degeneration of a polyp in the rectal pouch is well understood by the patients and it is hoped that frequent examinations will preclude this occurrence. Everson and Allen reviewed 115 cases of familial polyposis treated by subtotal colectomy and reported in the American literature. They noted that carcinoma of the rectum developed in 5.2 per cent of the collected cases in spite of periodic examination and treatment after subtotal colectomy had been performed. Patients with familial polyposis must be informed that preservation of normal bowel function by ileoproctostomy carries a calculated risk of carcinoma developing in the retained rectum.

DIVERTICULAR DISEASE OF THE COLON

Complications of diverticulosis of the colon occasionally require extensive resectional surgery. If melena occurs in a patient with diverticula distributed throughout the entire colon, the site of bleeding usually cannot be localized.

CASE 8. F. N., a 58 year old white male, was admitted to the Brooklyn Veterans Administration Hospital on November 12, 1953 because of a 2 day history of the passage of bright red blood per rectum. During the past 9 years he had had numerous similar episodes which, on 3 occasions, required hospitalization and multiple transfusions. The patient was in deep shock

FIG. 8. Case 8. Diffusely distributed diverticula of the colon seen on postevacuation study after barium enema.

on admission to the hospital and required 3 pints of blood to stabilize his blood pressure. Active bleeding stopped in 24 hours and 2 additional pints of blood were given to elevate his hemoglobin to a satisfactory level. After the clinical status was stabilized, barium enema disclosed the presence of diverticulosis of the entire colon (Fig. 8). Sigmoidoscopy revealed diverticula orifices on the anterior and lateral walls of the rectosigmoid 20 and 25 centimeters from the anus.

In view of the history of repeated massive hemorrhages, surgery was advised. On November 30, 1953, a subtotal colectomy with ileoproctostomy was performed with the anastomosis 15 centimeters from the anal verge. Examination of the resected specimen revealed diverticulosis of the entire colon, but the site of recent hemorrhage could not be determined. Since discharge the patient has been having 2 to 3 formed stools per day and there has been no further rectal bleeding.

The patient was readmitted on August 20, 1954 with acute mechanical intestinal obstruction secondary to an adhesive band. Surgical correction was performed and thereafter the course has been asymptomatic. The patient has maintained his weight and has no dietary restrictions.

This case demonstrates an infrequent yet serious complication of colonic diverticulosis. Subtotal colectomy and ileoproctostomy may be the only means of controlling recurrent or massive hemorrhage. The rectum is rarely the site of diverticula. Consequently, subtotal colectomy effects the removal of all the diverticula and yet preserves enough of the distal gastrointestinal tract to allow for normal function.

The surgical management of diverticulitis varies with the extent and location of the disease. In most cases the process is localized and can be treated by resection of a segment of the colon. Occasionally areas of diverticulitis may be scattered throughout the colon and require subtotal colectomy and ileoproctostomy.

POSTOPERATIVE BOWEL FUNCTION

The postoperative bowel function of the 8 patients reported in this article is demonstrated in Table I. The rectal segments that were preserved varied from 12.5 to 16 centimeters in length and the amount of ileum resected varied from 3 to 15 centimeters. This was sufficient to provide bowel function that closely approximated normal. All except 1 of our patients pass 1 to 3 semisolid or formed stools daily and have no urgency or cramps. The 1 patient with watery or semisolid stools is difficult to manage because he drinks an excessive amount of alcohol. A total of only 15 centimeters of his terminal ileum was resected and this loss should not cause postoperative diarrhea. The only incontinence in the series was in Case 5, the patient who had a cerebrovascular accident on the fourteenth postoperative day. All patients who were followed for long periods after the operation ate well and maintained or gained weight. Three patients noted an increased passage of flatus but this disturbance was not marked. These facts indicate that one can dispense with the colon down to the rectosigmoid and not disturb body function and economy.

The development of good bowel function after subtotal colectomy has 2 prerequisites, namely, an adequate rectal pouch, and preservation of terminal ileum. Gaston has shown that if the anal sphincter and at least 5 centimeters of rectal wall are preserved the patient can maintain sphincter continence and reservoir continence. Investigators

have recently stressed the importance of the distal ileum in water absorption, and report that sacrifice of excessive amount of ileum predisposes the patient to postoperative nutritional disturbance and diarrhea. Perry studied this problem in cats by perfusing various areas of the bowel with normal saline. He demonstrated that the terminal 12 centimeters of ileum had a water absorbing capacity 1.8 times greater than that of the entire colon. Lillehei and Wangensteen believe that bowel function after subtotal colectomy is usually normal if not more than 20 centimeters of terminal ileum is excised. They state that if no ileum is resected, diarrhea is practically nonexistent.

The immediate postoperative course after subtotal colectomy is characterized by a rather severe watery diarrhea which gradually disappears in 7 to 14 days. The terminal ileum is most efficient in absorbing fluids. Apparently, during this postoperative period it assumes an increased function to compensate for the loss of colonic absorption. In subtotal colectomies for conditions other than carcinoma of the right colon, the ileum can be preserved down to the terminal few centimeters. A few authors have advocated preservation of the ileocecal valve and anastomosis of the cecum to the rectum. Their data suggest that retaining this additional segment of the colon improves postoperative bowel function.

TECHNIQUE OF SUBTOTAL COLECTOMY

The technical aspects of subtotal colectomy have been widely published but a few details merit emphasis. The complete procedure is readily performed in one stage as blood loss should be minimal. A left rectus incision from the symphysis pubis to the region of the costal margin is necessary to facilitate mobilization of the flexures and also provide exposure for an anastomosis below the brim of the pelvis. Resection of the right, transverse, and left colon can be carried out close to the bowel wall, leaving the mesentery in situ. However, if the colon is widely mobilized the base of the mesentery can be transected and the entire mesentery removed with the colon. The latter method is our preference for a number of reasons. The smaller base of the mesentery can be more readily divided and ligated. A patient with multiple polyps or familial polyposis can occasionally harbor a minute malignant tumor which may not be detected by examination of the resected specimen. Patients with polyposis and no demonstrable cancer have died of metastases after total colectomies. If the indication for resection is potential malignancy, the patient is served best by removing the mesentery.

The resection is carried distally to the rectosigmoid. If the mesentery of the rectosigmoid and the presacral plexus are not disturbed the patient will have no alteration of sex function. End-to-end anastomosis at that level will leave 12.5 to 15 centimeters of rectum. This segment and the stoma are readily accessible to the sigmoidoscope.

CONCLUSIONS

1. Five cases of multiple polyps of the colon, 2 cases of familial polyposis, and 1 case of diverticulosis of the colon with massive hemorrhage were managed by subtotal colectomy and ileoproctostomy. Detailed histories and observations of postoperative bowel function of these 8 patients are presented.

2. Subtotal colectomy with ileoproctostomy usually results in the preservation of a normal state of nutrition and little or no abnormality in bowel function. This fact should encourage a wider utilization of the operation in the treatment of a variety of benign and malignant lesion of the colon.

3. Multiple polyps of the colon are treated most efficiently by subtotal colectomy with ileoproctostomy. This procedure effects removal of not only the detected polyps but also the variable number of hidden polyps that may be present. If carcinoma is found in any polyp in the resected specimen, the patient is already protected by an adequate radical resection of the colon.

4. Selected cases of familial polyposis of the colon may be managed by subtotal colec-

tomy and ileoproctostomy, but approximately 5 per cent will develop cancer in the retained rectal segment. This risk is the price that must be paid for retaining normal bowel function in preference to an ileostomy.

5. Some complications of diverticular disease of the colon can be most adequately treated by subtotal colectomy and ileoproctostomy. The operation removes all areas of disease and has no crippling effect on gastrointestinal function.

REFERENCES

1. Deddish, M. R., and Hertz, R. E. Colotomy and coloscopy in the management of polyps and cancer of the colon. Am. J. Surg., 1955, 90: 846.
2. Everson, T. C., and Allen, H. J. Subtotal colectomy with ileosigmoidostomy and fulguration of polyps in retained colon. Arch. Surg., 1954, 69: 806.
3. Gaston, E. A. Physiological basis for preservation of fecal continence after resection of rectum. J. Am. M. Ass., 1951, 146: 1486.
4. Judd, E. S., Jr., and Carlisle, J. C. Polyps of the colon. Late results of transcolonic removal. Arch. Surg., 1953, 67: 353.
5. Lillehei, R. C., and Wangensteen, O. H. Bowel function after colectomy for cancer, polyps and diverticulitis. J. Am. M. Ass., 1954, 159: 163.
6. Mayo, C. W., and Schlicke, C. P. Carcinoma of the colon and rectum: a study of metastases and recurrences. Surg. Gyn. Obst., 1942, 74: 83.
7. Perry, J. F., Jr. Comparative studies of the water absorbing capacity of the distal small intestine and the colon. Presented at the 41st Clinical Congress, American College of Surgeons, October 31, 1955.
8. Rider, J. A., Kirsner, J. B., Moeller, H. C., and Palmer, W. L. Polyps of the colon and rectum; their incidence and relationship to carcinoma. Am. J. Med., 1954, 15: 555.

STRUCTURAL ALTERATIONS IN HUMAN AORTIC HOMOGRAFTS ONE TO TWO AND ONE-HALF YEARS AFTER TRANSPLANTATION

OSCAR CREECH, JR., M.D., F.A.C.S., MICHAEL E. DE BAKEY, M.D., F.A.C.S., DENTON A. COOLEY, M.D., F.A.C.S., and BÉLA HALPERT, M.D., Houston, Texas

THE REDISCOVERY of arterial homografts within the past decade has made possible surgical correction of a number of vascular disorders. Although the functional results have been satisfactory, little is known about the ultimate fate of these transplants. Observations on experimental homografts disclosed a gradual deterioration within the media after 1 year and it has been assumed that similar changes would occur also in human transplants. However, in a recent study of 10 human aortic homografts 1 day to 1 year after transplantation the elastic fibers remained intact and new inner and outer coats were formed from fibrous connective tissue (1, 4). In these grafts there were no changes suggestive of early structural failure.

Now, 4 additional human aortic homografts have become available 14, 24, 28, and 30 months, respectively, after transplantation. The alterations observed in these transplants provide further information concerning the natural history of human arterial homografts.

CASE REPORTS

Homograft 14 Months After Transplantation

R. H., a 55 year old white man, was admitted to Methodist Hospital December 28, 1949, for treatment of an abdominal aortic aneurysm. Two days later a celiotomy was performed, the aneurysm was wrapped in reactive polythene film, and a rubber catheter was tied about the aorta proximal to the aneurysm to reduce the lumen. Following operation there was moderate relief for about 6 months when symptoms recurred and the abdominal aneurysm began to increase in size. On May 24, 1953, the patient was readmitted to the hospital, and the aneurysm was excised and replaced with a refrigerated bifurcation homograft. This homograft was obtained from the abdominal aorta of a 26 year old negro man who died suddenly during induction of anesthesia for excision of tuberculous cervical lymph nodes. The aorta was removed aseptically 6 hours after death, the body having been refrigerated during the interval at about 5 degrees C., and the graft was kept in a modified Tyrode's solution at 4 degrees C. until its use 3 days later.

Convalescence was uneventful and the patient was discharged June 4, 1953. He was relatively symptom-free until August, 1954, when he died of coronary occlusion with massive myocardial infarction.

At necropsy the graft was of normal size with its lumen patent. A dense fibrous connective tissue surrounded it and obscured the lines of anastomosis. On the left where the graft had been anastomosed to the external iliac and hypogastric arteries, the hypogastric artery was occluded. The left external iliac and the right common iliac anastomoses were patent. The inner surface of the graft was smooth with delicate fibrin deposits in places. The graft was soft and pliable though occasional focal areas were somewhat thickened and firm.

Microscopically, suture material at the proximal anastomosis was enclosed in pink amorphous substance that was surrounded by a zone infiltrated with lymphocytes, plasma cells, large mononuclear cells, and giant cells of the foreign-body type. Near the anastomosis the intima was delimited by flat cells with nuclei at regular intervals (Fig. 1). Beneath this endothelial lining was a broad zone of fibrous connective tissue with elongated cell nuclei bordered by a zone of elastic fibers comprising the media. In this no nuclear staining was discernible. The adventitia was composed of coarse collagenous bundles containing focal and diffuse infiltrations of lymphocytes, plasma cells, and large mononuclear cells. In a Weigert prepara-

From the Cora and Webb Mading Department of Surgery and the Department of Pathology, Baylor University College of Medicine, and the surgical services of the Jefferson Davis, Methodist, and Veterans Administration Hospitals, Houston, Texas.

This study was supported in part by the Houston Heart Association.

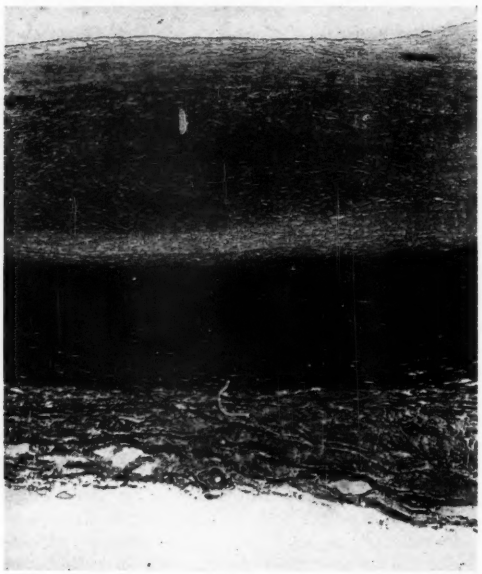


FIG. 1.

FIG. 1. Abdominal aortic homografts 14 months after transplantation (Case 1). Near the line of anastomosis a broad zone of fibrous connective tissue with elongated cell nuclei forms the intima. There is no inner elastic lamina. The media is of elastic fibers and adventitia of coarse collagenous bundles. Weigert's preparation, ×16.

FIG. 2. Abdominal aortic homograft 14 months after transplantation (Case 1). In the midportion of the graft the intima consists of a fibrillar substance with occasional cell nuclei and is demarcated sharply from the elastic fibers of the media. The elastic fibers of the media are disrupted by an atheromatous plaque. Trichrome preparation, ×40.

FIG. 2.

tion, elastic fibers were prominent in the media but a distinct inner elastic lamina was not evident. In the midportion of the graft the intima consisted of a fibrillar substance with occasional cell nuclei and was demarcated sharply from the elastic fibers of the media (Fig. 2). There was no cellular infiltration in the media, and in occasional areas the elastic fibers were disrupted. At these sites of discontinuity of the elastic fibers there were cholesterol clefts. These deposits extended toward the intima and in some places communicated with the inner surface of the graft. In the host vessels adjacent to the proximal and distal anastomoses there was extensive atheromatous change in the intima and media.

Homograft 24 Months After Transplantation

J. M., a 46 year old negro man, was admitted to Jefferson Davis Hospital July 4, 1951, with an aneurysm of the innominate artery presumed to be syphilitic. On July 12 the aneurysm was excised and lateral aortorrhaphy performed. During his hospital stay an aneurysm of the abdominal aorta was discovered. On November 29 this aneurysm was wrapped with reactive polythene film. On January 8, 1953, because of continued abdominal pain and increase in size of the aneurysm, celiotomy was performed, revealing that the aneurysm had increased in size and that the polythene film had induced little reaction. The aneurysm together with the aortic bifurcation was excised and replaced with a refrigerated homograft. This homograft was obtained from a 27 year old man who died of a gunshot wound of the chest. The aorta was aseptically obtained 4 hours post mortem and was refrigerated in modified Tyrode's solution at 5 degrees C. until its use 21 days later.

Following operation the patient was free of symptoms and remained well until January 30, 1955, when he was readmitted to the hospital in cardiac failure and died.

At necropsy the thoracic aortorrhaphy was well healed. Its inner surface was covered by a laminated thrombus. There was marked cardiac hypertrophy and dilatation, the heart weighing 720 grams. The homograft in the abdominal aorta revealed saccular dilatations at each of the anastomoses of the graft to the host vessels. It was patent. The proximal dilatation was 4 by 4 centimeters, the dilatations in the common iliac arteries were 5 by 5 centimeters. On the

FIG. 3.

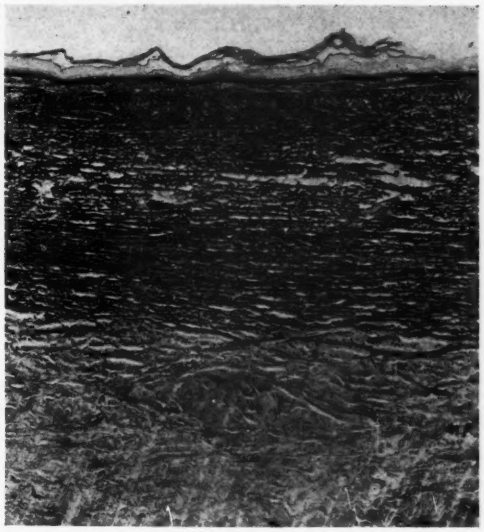


FIG. 4.

FIG. 3. Aortorrhaphy in the arch 3½ years after operation (Case 2). The intima is broadened by atheromatous change replacing the media and bordered by a narrow vascular adventitia. Trichrome preparation, ×7.

FIG. 4. Abdominal aortic homograft 24 months after transplantation (Case 2). In the midportion of the graft the intima consists of a narrow band of fibrillar substance. A distinct inner elastic lamina demarcates the intima from the media. Here the elastic fibers are spread apart and frequently interrupted. The adventitia is made up of coarse collagenous bundles. Weigert preparation, ×40.

intimal surface of the graft patches of atheromatous change were noted and a layer of fibrin partially covered the intima. There were saccular dilatations only at the suture lines. They were filled with laminated thrombi so that the inner diameter of the graft remained unchanged although the external diameter was considerably increased.

Microscopically, the aortic arch at the site of aortorrhaphy revealed a broadened intima that contained many large mononuclear cells with foamy cytoplasm and spaces filled with fibrillar acellular substance (Fig. 3). These areas were contiguous with pink amorphous fields with slit-like spaces and deposits of blue granular material that protruded into the lumen, replacing the media, and contiguous with areas of extravasated erythrocytes in the adventitia. Elsewhere in the adventitia there were many wide endothelial lined spaces surrounded by infiltrations of lymphocytes, plasma cells, and occasional large mononuclear cells.

In the abdominal aortic homograft at the lines of anastomosis there was thinning of the wall by marked narrowing of the media in both host and graft portions. In the host atheromatous change replaced the intima and parts of the media to which was attached a laminated thrombus filling the aneurysm. In the midportion of the graft the intima was made up of a narrow band of fibrillar substance demarcated toward the media by closely packed elastic fibers (Fig. 4). In the media proper elastic fibers were discernible. They were bordered externally by coarse collagenous bundles of fibrous connective tissue. In the Weigert preparation the media was composed of elastic fibers that were spread apart with frequent discontinuities. Elsewhere focal atheromatous changes were noted in the intima and media.

Homograft 28 Months After Transplantation

N. J. T., a 49 year old white man, was admitted to Methodist Hospital June 6, 1953, because of severe pain in the lumbosacral region. Examination disclosed a large aneurysm of the abdominal aorta. On July 10 the aneurysm was resected and replaced with a freeze-dried bifurcation aortic homograft. This graft was obtained during routine necropsy and was sterilized with ethylene oxide. After lyophilization it was stored at room temperature until use. The postoperative course was uneventful and the patient was discharged July 20. On November 5, 1955, he was readmitted with a left hemiplegia and died on November 9.

Necropsy revealed thrombosis of the right internal carotid artery with encephalomalacia, an acute ulcer of the duodenum with gastrointestinal hemorrhage, cardiac hypertrophy, and focal pneumonia. The abdominal aortic homograft was intact and patent. The graft was 10 centimeters long, the abdominal aortic portion being 8 centimeters and the common iliac arteries 2 centimeters each. It was surrounded by fibrous connective tissue that obscured the suture lines. There were extensive atheromatous changes in

FIG. 5.

FIG. 5. Abdominal aortic homograft 28 months after transplantation (Case 3). Near the anastomosis there is an atheromatous plaque in the intima and media. In its center are detached elastic fibers. Nearby there are calcific deposits and in the host portion bony trabeculae with marrow spaces. Weigert preparation, ×10.

FIG. 6. Enlarged view of the atheromatous plaque in Figure 5. Detached elastic fibers in the center of the plaque. ×83.

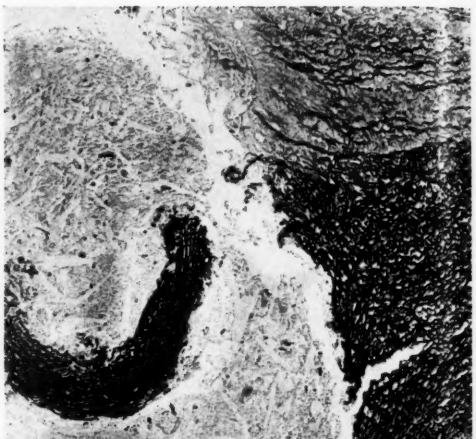


FIG. 6.

the aorta and common iliac arteries above and below the graft and these appeared to extend across the suture lines onto the surface of the graft. On the inner surface the graft was covered with a thin layer of fibrin-like material beneath which were focal atheromatous plaques. There was no dilatation of the graft.

Microscopically, a zone of pink amorphous substance with abundant empty spaces containing some cell nuclei formed the intima over the graft. The substance was somewhat increased in width toward and over the suture line and the host aorta. In these areas an intima containing many foam cells with eccentrically placed nuclei was as wide as or wider than the overlying zone of amorphous pink substance. The media of the graft contained closely packed fibrils which varied in texture adjacent to the intima. This zone was half as wide as the amorphous substance covering it. There was a blending of the acellular media with the media of the aorta. In the latter, slit-like spaces were frequent, and there were areas of hyalinized fibrous connective tissue around blood vessels and streaks of infiltration with lymphocytes, plasma cells, and large mononuclear cells. In some fields there was amorphous substance with slit-like spaces replacing over half of the media and part of the intima. An adventitia almost the width of the graft media and composed of coarse collagenous bundles continued beyond the suture line into the adventitia of the host aorta. In another preparation near the lines of anastomosis there were giant cells of the foreign body type surrounding double refractile suture material. Nearby in the host aorta there were deposits of calcium and bony trabeculae with Haversian systems (Fig. 5). These enclosed marrow spaces containing adult adipose tissue cells and marrow cells. In the graft media near the anastomosis there was an area of atheromatous change extending to the intima and almost to the adventitia. This consisted of an amorphous substance with slit-like spaces and pink coagulum with some granules of blue material. This atheromatous change disrupted or involved almost the entire width of the media (Fig. 6). Distal to this area focal deposits of blue granular substance were seen. In trichrome and Weigert preparations these changes were even more clearly discernible.

In the middle of the graft the intima was made up of a wavy fibrillar substance sharply demarcated from the subjacent acellular media (Fig. 7). In the latter there was a central loose fibrillar portion with clear spaces that extended over the length of a microscopic field. An atheromatous plaque was noted composed of amorphous substance with some foam cells. The elastic fibers were disrupted. Nearby, the adventitia was studded in its external portion by abundant lobules of adult adipose tissue cells containing many nerve

bundles and a sympathetic ganglion. In the distal anastomosis the changes were essentially similar to those seen about the proximal anastomosis.

Homograft 30 Months After Transplantation

H. H. D., a 67 year old white man, was admitted to Methodist Hospital February 18, 1953, for treatment of an abdominal aortic aneurysm. He had complained of severe abdominal and back pain for 4 years; however, the diagnosis of aortic aneurysm had been established only 6 months previously. At operation on February 24, 1953, the aneurysm was 12 by 7 centimeters and extended from below the renal arteries to 1 centimeter above the aortic bifurcation. The segment of abdominal aorta with the aneurysm was removed and replaced by a refrigerated homograft. This graft was from a 26 year old negro man who died of a stab wound of the left chest which divided the anterior descending branch of the left coronary artery and entered the left ventricle. The graft was obtained 5 hours post mortem and was refrigerated in modified Tyrode's solution until its use 3 days later.

Convalescence was uneventful and the patient was discharged on March 16. In spite of severe hypertension he remained well until August 15, 1955, when he suddenly died. It was presumed that coronary occlusion was the cause of death. Authorization for postmortem examination was limited to the abdomen.

At necropsy the abdominal aorta was densely adherent to the surrounding tissues. The graft was of usual diameter. Immediately above it there was a saccular aneurysm 5 centimeters in diameter containing a laminated thrombus. The left and right common iliac arteries were moderately dilated and a small aneurysm involved the right common iliac artery near its bifurcation. Opening the aorta along its posterior aspect revealed the luminal surface to be smooth in sharp contrast with the marked atherosclerotic changes in the aorta and iliac arteries proximal and distal to the graft (Fig. 8).

Microscopic examination of the proximal anastomosis revealed residual suture material surrounded by giant cells of the foreign body type. The junction of the graft and aorta was marked by fibrinoid substance which thinned and disappeared over the surface of the graft. The elastic fibers of the media of both graft and aorta were absent at the anastomotic line, being replaced by scar tissue. In the graft near the proximal anastomosis the intima was one-half the width of the media and its inner and outer surfaces were delimited by wavy lines. Over part of the surface, nuclei were discernible in the intima and in places appeared to be elongated (Fig. 9). Elsewhere, the intimal surface consisted of amorphous pink substance resting on elastic fibers of the media. There were no cell nuclei discernible in the media and the elastic fibers were closely packed with no evidence of fragmentation. The adventitia was about one-third

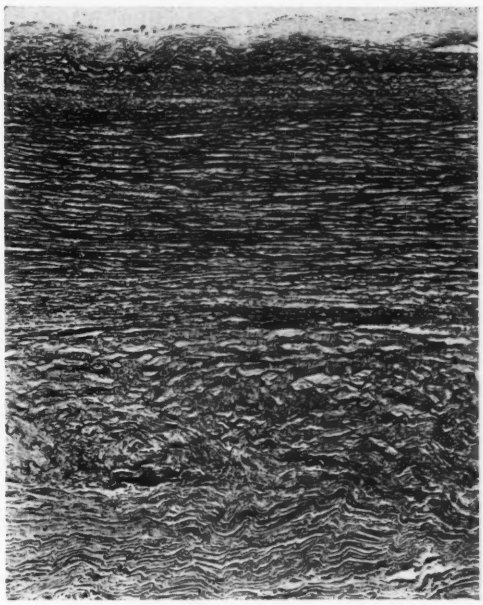


FIG. 7. Abdominal aortic homograft 28 months after transplantation (Case 3). In the middle of the graft the intima is composed of a wavy fibrillar substance demarcated from the intact media by an inner elastic lamina bordered by the adventitia. Weigert preparation, ×40.

wider than the media and intima and was composed of coarse collagenous bundles. In the periphery of the adventitia there were infiltrations of lymphocytes, plasma cells, and large mononuclear cells. Similar changes were noted at the distal anastomosis. In the trichrome preparation the pattern described was more clearly discernible. In the Weigert preparation the elastic fibers of the graft were closely packed, wavy, and appeared to be intact. The elastic fibers bordering the inner surface were stained somewhat lighter than those elsewhere. At the distal suture line suture material was surrounded by giant cells of the foreign body type. The intima in places was overlaid by a fibrinoid substance. The luminal surface appeared to be made up of a condensation of wavy elastic fibers. In the midportion of the graft the intimal surface was formed by closely packed elastic fibers of the media (Fig. 10). Elsewhere scattered cell nuclei were evident in a thin layer of fibrinoid material. The elastic fibers were closely packed and appeared relatively unchanged. The adventitia was broadened by coarse collagenous bundles containing infiltrations with lymphocytes, plasma cells, and large mononuclear cells. Although atheromatous and sclerotic changes were extensive in the aorta, no such changes were seen in the graft.

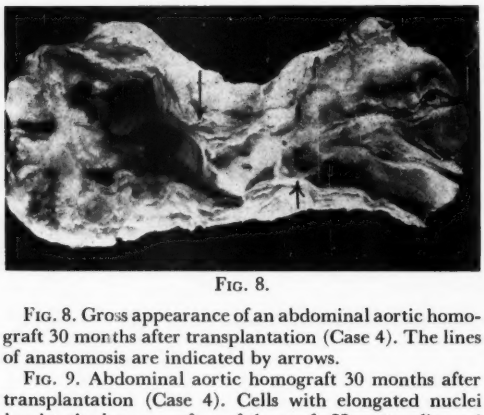


FIG. 8.

FIG. 8. Gross appearance of an abdominal aortic homograft 30 months after transplantation (Case 4). The lines of anastomosis are indicated by arrows.

FIG. 9. Abdominal aortic homograft 30 months after transplantation (Case 4). Cells with elongated nuclei border the lumen surface of the graft. Hematoxylin and eosin preparation, ×324.

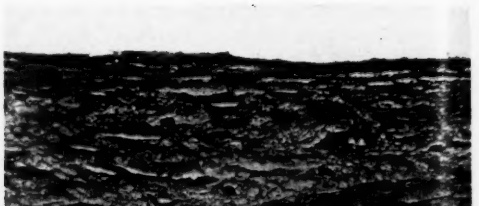


FIG. 9.

COMMENT

The gross and microscopic observations on the 4 aortic homografts that were in place longer than 1 year tend to confirm those previously made (1, 4), namely, that the human aortic homograft becomes functionally and structurally adapted to its new environment. The structural alterations in the homograft occur gradually and consist of retention of the media and formation of a new intima and a new adventitia. The intimal surface of the homograft is not covered by a continuous endothelial lining. Near the suture lines and for varying distances toward the midportion of the graft the intima is cellular. In parts an amorphous fibrinoid substance covers the surface and elsewhere the fibers of the media border the inner surface. The media is narrowed by condensation of the elastic fibers and apparent loss of its ground substance. On the outside the vessel wall becomes fortified by hyalinizing fibrous connective tissue that forms a new adventitia.

The completeness of the local adjustment has been demonstrated in 3 patients still living. In these, abdominal exploration was performed 1 to 1½ years after resection and replacement by homograft of an abdominal aorta. During the course of operation examination of the aorta revealed that the homograft had the same texture and pulsatile expansion of the rest of the aorta.

It should be emphasized that the arterial homograft is not replaced by scar tissue as was asserted previously (2, 4, 5). Indeed, the homograft retains much of its architectural pattern while it is being reinforced by fibrous connective tissue of the host. Its adaptation as a conduit in a new host is apparently accomplished without complete loss of its structural identity.

In the grafts 14, 24, and 28 months old, some changes in the media were noted that did not appear in the younger grafts. The changes consisted of focal fragmentation of elastic fibers and disruption of them by cholesterol clefts and scattered deposits of calcium, apparently an atherosclerotic process.

The possibility has been anticipated that atheromatous changes might occur in a homograft when planted into a host with atherosclerosis. In addition to the adaptive changes that occur in the graft and the wear and tear to which it is subjected as part of the arterial system the homograft is exposed to the same environmental factors as the host aorta. Indeed, in recent experiments canine aortic homografts were shown to be sites of predilection for the appearance of atherosclerotic changes in animals with induced hypercholesterolemia (3). It was demonstrated that in those dogs with serum cholesterol levels of 1,000 milligrams per

100 cubic centimeters or more, the host aorta and abdominal aortic homograft alike developed atheromatous change. In those animals with cholesterol levels less than 1,000 milligrams per 100 cubic centimeters only the homograft was involved. The results were similar whether the homografts were preserved by refrigeration or freeze-drying.

The retrogressive changes noted in the grafts 14, 24, and 28 months old were not seen in the graft examined 30 months after transplantation. The difference between these homografts was their length: the younger grafts were long and the oldest was short and did not include the bifurcation. In the graft examined previously after 1 year no retrogressive changes were noted (1, 4, 5). In fact, the architectural pattern of this was strikingly similar to that of the graft 30 months old. This younger graft included the aortic bifurcation, but consisted of two segments because of removal of a redundant portion of the graft at the time of implantation. Thus the situation was similar to that in short grafts, namely, the opportunity for fibrous connective tissue to invade the entire segment from the lines of anastomosis. This circumstance apparently affords a more rapid vascularization of the graft, furthering the adaptive process.

The possibility that early atheromatous changes might have been present in the grafts at the time of implantation should be considered. However, the age of the donors and lack of gross evidence of such change at the time of procurement makes this unlikely. In the 24 months old homograft (Case 2) aneurysmal dilatation occurred at the sites of anastomosis. Since they involved equally the adjacent portions of the host aorta and the homograft, it is doubtful whether their occurrence can be related directly to changes in the graft.

While the structural changes occurring in the graft are of interest, they bear no apparent relation to the function of the homograft. Thus, in an experience with more than 400 cases of aortic resection and homograft replacement covering a period of 3½ years the grafts have continued to function satisfactorily in patients who survived the operation. To be sure, many of the homografts may have undergone changes similar to those just recorded. In fact, calcific changes have been observed by Gross several years after transplantation. Yet, in his and in our experience this does not interfere with the function of the graft.

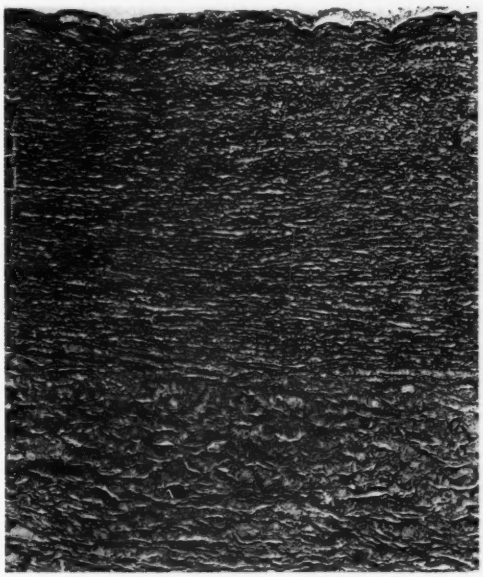


FIG. 10. Abdominal aortic homograft 30 months after transplantation (Case 4). In the midportion of the graft the intimal surface is bordered by closely packed elastic fibers. The elastic fibers of the media are intact. Weigert preparation, ×40.

Time alone will provide the answer to the ultimate fate of aortic homografts. In the meantime it is an effective means of treating a variety of lesions of the aorta and on the basis of our experience the aortic homograft can be used with confidence.

SUMMARY

Gross and microscopic studies are recorded in 4 human aortic homografts 14, 24, 28, and 30 months, respectively, after transplantation. These confirm the observations previously made that the human aortic homo-

graft becomes functionally and structurally adapted to its new environment, and that the homograft retains much of its structural pattern while it is being reinforced by the fibrous connective tissue of the host. Alterations observed in the grafts 14, 24, and 28 months old were not present in the graft 30 months after transplantation. The difference was apparently due to the fact that the younger grafts were long, and the oldest was short and did not include the bifurcation. The ultimate fate of aortic homografts is as yet not known. In the meantime, this procedure is an effective means of treating a variety of lesions of the aorta, and based on the experience to date the aortic homograft can be utilized with confidence.

REFERENCES

1. Creech, Oscar, Jr., De Bakey, Michael E., and Cooley, Denton A. Substitutes for arterial segments. Cardiovascular Surgery. Proceedings of the Symposium held at Henry Ford Hospital, Detroit, Michigan, March, 1955. Edited by Conrad R. Lam, M.D. Pp. 504-508. Philadelphia: W. B. Saunders Co., 1955.
2. Creech, Oscar, Jr., De Bakey, Michael E., Self, Milton, and Halpert, Béla. The fate of heterologous arterial grafts. Surgery, 1954, 36: 431–433.
3. Creech, Oscar, Jr., Jordan, George L., De Bakey, Michael E., Overton, Robert C., and Halpert, Béla. The effect of chronic hypercholesterolemia on canine aortic transplants. Surg. Gyn. Obst., 1955, 101: 606–614.
4. De Bakey, Michael E., Creech, Oscar, Jr., Cooley, Denton A., and Halpert, Béla. Structural changes in human aortic homografts. Arch. Surg., 1954, 69: 472–482.
5. De Bakey, Michael E., Creech, Oscar, Jr., and Halpert, Béla. Regeneration of the elements of the vessel wall. Symposium on Atherosclerosis, Pub. 338 of National Academy of Sciences. Pp. 103–111. National Research Council, 1954.
6. Gross, R. E. Discussion of paper by Creech (2).

FREEZE-DRIED AND ALCOHOL PRESERVED HOMOGRAFTS FOR REPLACEMENT OF SMALL ARTERIES

THOMAS C. MOORE, M.D., F.A.C.S., ANGELO RIBERI, M.D., and
HISASHI KAJIKURI, M.D., Indianapolis, Indiana

THE RAPID ADVANCES which have been made in vascular surgery in recent years have increased markedly the demands for arterial substitutes. Tubes from anatomic structures, in a fresh or preserved state, and those constructed from a number of synthetic plastic materials have been used most frequently in laboratory and clinical studies. Although freeze-dried arterial homografts and plastic grafts have achieved the greatest popularity at the present time, it is apparent that more time and study will be required to evaluate properly the suitability of the various substitutes and means of preservation currently in use.

The bulk of contemporary laboratory effort has been directed toward the replacement of large vessels, principally the aorta. In this area, a relatively high degree of success may be obtained with many of the various types of grafts. Indeed, at times, it is difficult to demonstrate a clear and convincing superiority of one of these materials over another. The same is true of homografts with respect to some of the different methods of graft preservation. In these instances, certain practicalities relative to the expense and convenience of obtaining and preserving the grafts and to the technical ease of their insertion assume greater importance.

The problems of small artery grafting have received relatively little attention in recent years, due largely to pressing clinical demands for more basic information concerning large vessel replacement. To be sure, some of the problems encountered in large vessel replacement exist to a magnified degree in small artery grafting. This is especially true with respect to thrombotic occlusion. For this reason, small vessels would appear to provide a rather critical testing ground for the various types of graft materials and methods of preservation and insertion now available. There also appears to be a real need for more careful study of the means of achieving reliable small artery replacement and by-pass.

The purpose of this investigation was to consider some of the problems encountered in the replacement of segments of small arteries and to compare the results with freeze-dried and alcohol preserved homografts. This report concerns the experience with 111 freeze-dried and alcohol preserved homografts which were used to replace segments of carotid and femoral arteries in dogs. It deals principally with short term results with emphasis on the capacity of the graft materials to retain their patency.

MATERIALS AND METHODS

The homografts were obtained from healthy mongrel dogs which were being sacrificed to obtain blood for another experiment. Initial efforts to use dog femoral ateries as homografts proved unsatisfactory because of the difficulty in obtaining sufficiently long segments which could be used with ease. The significant diminution in the caliber of the dog femoral artery progressing distally and the number of small tributaries from it were the major sources of trouble. For this reason, dog carotid arteries were used in all experiments as homografts for re-

From the Department of Surgery, Indiana University Medical Center, Indianapolis, Indiana.

Supported in part by a grant from the James Whitcomb Riley Memorial Association and a contract between the Office of Naval Research, United States Navy, and Indiana University.

TABLE I.—SUMMARY OF EXPERIENCE WITH FREEZE-DRIED HOMOGRAFT REPLACEMENT OF CAROTID ARTERY

Dog No.	Duration of placement, days	Weight of dog, kgm.	Died or sacrificed	Right carotid		Left carotid	
				Length of graft, cm.	Necropsy status	Length of graft, cm.	Necropsy status
164	3	7	D	4.2	Patent	4.2	Patent
282	5	11	D	5.0	Occluded	5.5	Occluded
331	22	10	S	5.0	Patent	5.5	Patent
304	35		S	5.7	Patent	6.6	Patent
315	36	9	S	5.6	Occluded	5.2	Patent
332	49	9	S	6.0	Patent	5.0	Patent
316	50	12	S	5.8	Patent	5.4	Patent
281	56	11	S	5.3	Occluded	6.2	Occluded
145	68	10	D		Occluded		Patent
295	70	13	S	6.1	Occluded	6.0	Occluded
231	119	10	S	6.0	Occluded	4.5	Occluded
163	175	5	S	4.3	Patent	4.4	Patent
144	189	13	S		Patent		Occluded

TABLE II.—SUMMARY OF EXPERIENCE WITH FREEZE-DRIED HOMOGRAFT REPLACEMENT OF FEMORAL ARTERY

Dog No.	Duration of placement, days	Weight of dog, kgm.	Died or sacrificed	Right femoral		Left femoral	
				Length of graft, cm.	Necropsy status	Length of graft, cm.	Necropsy status
164	3	7	D	3.9	Occluded	3.1	Occluded
282	5	11	D	5.0	Patent	5.6	Patent
331	22	10	S	4.5	Patent	4.4	Patent
304	35		S	6.3	Patent	5.3	Patent
315	36	9	S	6.8	Occluded	5.8	Occluded
332	49	9	S	5.0	Patent	5.0	Occluded
316	50	12	S	5.0	Patent	5.2	Patent
281	56	11	S	5.7	Occluded	4.9	Patent
145	68	10	D		Patent		Occluded
295	70	13	S	6.3	Occluded	5.8	Occluded
231	119	10	S	5.5	Occluded	5.0	Occluded
144	189	13	S		Patent		Occluded

placement of both femoral and carotid arteries.

Two types of preservation were used. The freeze-dried grafts were removed in a nonsterile manner and sterilized in an ethylene oxide solution prior to lyophilization. They were stored at room temperature in sealed glass cylinders containing nitrogen gas. The alcohol grafts also were obtained by a nonsterile technique. They were stored in a sterile container in a solution of 70 per cent ethyl alcohol. The alcohol served both as a sterilizing and preserving agent. Both freeze-dried and alcohol preserved grafts were reconstituted prior to use by immersion for 1 hour in a warm isotonic saline solution containing penicillin and streptomycin.

Healthy mongrel dogs were used as recipients of the homografts. The weight of the dogs ranged from 5 to 14 kilograms and averaged 10 kilograms. In the majority of the animals, 4 grafts were employed to replace carotid and femoral arteries bilaterally. The sites of intended incision over the carotid and femoral arteries were shaved and prepared by mechanical scrubbing with ether, *p*Hisohex, zephiran chloride, and merthiolate,

Segments of femoral and carotid arteries averaging slightly over 5 centimeters in length were resected and replaced with a homograft. Deknatel No. 6-0 arterial silk suture was used for the anastomoses which were carried out end-to-end. An initial everting mattress suture was placed and carried on as a continuous over-and-over suture around the entire anastomosis. Meticulous technique and rigid asepsis were observed throughout. Anticoagulants were not used during or following operation. Penicillin was given intramuscularly following operation and for 2 days thereafter.

FREEZE-DRIED HOMOGRAFTS

Carotid grafts. Twenty-six freeze-dried homografts were used to replace a resected

FIG. 1.

FIG. 1. Arteriogram showing bilateral patency of arterial homografts which were used to replace resected segment of carotid artery bilaterally in 13 dogs (Table I). The homografts averaged 5.3 centimeters in length and were used to replace resected segments of approximately equal length. The average weight of the dogs was 9.9 kilograms.

Relatively little difficulty was encountered in achieving accurate end-to-end approximation without constriction at the anastomotic site. The No. 6-0 arterial silk suture seemed well suited for this type of anastomosis. The proximal and distal cut ends of the host carotid artery were occluded with straight Potts coarctation clamps. Upon completion of the anastomoses and release of the clamps, more bleeding was encountered at the suture lines than generally has been encountered by us in the placement of the larger aortic homografts in dogs. An attempt was made early in this study to reduce the amount of suture line bleeding by placing the continuous sutures closer together. This was only partially successful. Attempts to use additional interrupted sutures seldom helped and often merely made matters worse by producing 2 new needle holes in the vessel wall. The greater amount of bleeding at the suture line in these relatively thin-walled arteries as compared with the aorta presumably results from the greater ease of securing a watertight approximation of the ends of the larger, thicker-walled vessels. In some instances, small strips of gelfoam were wrapped around the suture lines. However, in most cases the bleeding was controlled simply by permitting the vessel

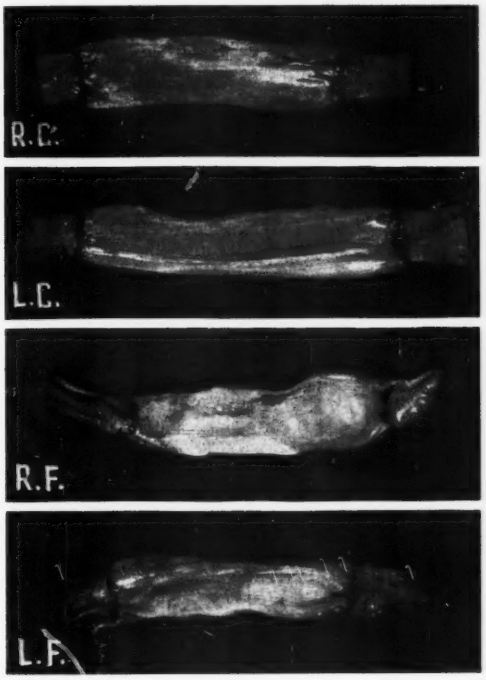


FIG. 2.

FIG. 2. Appearance at necropsy of 4 small freeze-dried homografts 35 days after insertion. All of the grafts, both to femoral and carotid arteries, were patent and functioned satisfactorily.

TABLE III.—SUMMARY OF EXPERIENCE WITH ALCOHOL PRESERVED HOMOGRAFT REPLACEMENT OF CAROTID ARTERY

Dog No.	Duration of placement, days	Weight of dog, kgm.	Died or sacrificed	Period of storage in alcohol, days	Right carotid		Left carotid	
					Length of graft, cm.	Necropsy status	Length of graft, cm.	Necropsy status
209	8	8	D	12	5.5	Patent	5.0	Patent
210	10	7	D	12	4.5	Patent	5.0	Patent
374	11	14	S	30	5.2	Occluded	6.2	Occluded
351	14	10	S	60	5.3	Patent	5.4	Patent
252	39	11	S	60	6.0	Occluded	5.5	Patent
259	77	9	S	30	4.0	Patent	4.2	Patent
251	84	10	S	8	4.7	Occluded	5.3	Occluded
270	84	9	S	36	5.0	Patent	5.0	Occluded
258	98	9	S	30	4.7	Patent	5.3	Occluded
242	111	11	S	6	6.0	Patent	5.0	Patent
243	111	11	S	6	5.0	Patent	5.6	Patent
220	113	11	S	6	5.0	Occluded	6.2	Occluded
219	133	12	S	6			6.2	Occluded
192	154	8	S	10	6.5	Patent	5.5	Patent
153	182	10	S	7	5.0	Patent	4.5	Occluded
154	182	10	S	7	4.5	Patent	4.5	Patent

and graft to return to the vascular bed. The amount of bleeding was essentially the same with carotid and femoral grafts, and the method of preserving the homograft did not seem to alter it.

The principal problem arising at the time of operation involved thrombotic occlusion of the graft shortly after completion of the anastomosis, before closure of the incision. This occurred rather frequently and with both types of graft material. In most cases, the fresh clot could be broken up by digital manipulation and adequate pulsation could be restored. On occasion, this maneuver had to be repeated several times. This observation leads us to believe that most grafts which become occluded by thrombus formation do so within relatively short periods after placement. The thin walls of the small artery grafts made it relatively easy to detect the presence of an early, soft thrombus.

Three dogs died and 10 were sacrificed. Graft difficulties were not responsible for any of the deaths. Infection was not found in any of the graft areas. There was no instance of suture line or graft rupture and no evidence of aneurysmal dilatation in any of the grafts. There were no hematomas. Fifteen of the grafts were patent and functioning (57 per cent) and 11 were occluded. Arteriograms were made prior to sacrifice in some animals and were of assistance in demonstrating both the functional patency of the grafts and the absence of aneurysmal dilatation (Fig. 1). A tiny mural thrombus was found on the wall in 2 of the patent grafts. All of the remaining

TABLE IV.—SUMMARY OF EXPERIENCE WITH ALCOHOL PRESERVED HOMOGRAFT REPLACEMENT OF FEMORAL ARTERY

Dog No.	Duration of placement, days	Weight of dog, kgm.	Died or sacrificed	Period of storage in alcohol, days	Right femoral		Left femoral	
					Length of graft, cm.	Necropsy status	Length of graft, cm.	Necropsy status
209	8	8	D	12	4.0	Patent	4.5	Patent
210	10	7	D	12	4.7	Occluded	4.7	Occluded
374	11	14	S	30	5.4	Occluded	5.2	Patent
351	14	10	S	60	4.8	Patent	4.0	Patent
252	39	11	S	60	5.0	Patent	5.5	Occluded
259	77	9	S	30	3.5	Occluded	3.0	Patent
251	84	10	S	8	3.7	Occluded	3.6	Occluded
270	84	9	S	36	4.0	Patent	4.8	Patent
258	98	9	S	30	4.0	Occluded	4.5	Occluded
242	111	11	S	6	4.6	Occluded	5.0	Patent
243	111	11	S	6	5.0	Patent	5.2	Patent
220	113	11	S	6	3.0	Occluded	4.3	Occluded
219	133	12	S	6	6.0	Patent	5.6	Occluded
192	154	8	S	10	6.5	Occluded	5.5	Patent
154	182	10	S	7	6.8	Occluded	6.7	Occluded

patent grafts appeared well endothelialized and remarkably free of any blemishes (Fig. 2). There did not appear to be any correlation between the incidence of thrombotic occlusion and the length of the graft or the duration of placement, within the limits of this experiment. This seemed to be true of both types of grafts and in both areas grafted.

Femoral grafts. Freeze-dried homografts were used to replace a portion of the femoral artery bilaterally in 12 dogs (Table II). All 24 homografts inserted were carotid arteries. The grafts averaged 5.2 centimeters in length.

Some mild disparity in size often existed between the graft and the host artery. This generally was more noticeable at the distal anastomosis where the lumen of the femoral artery tended to be smaller than at the level of the proximal anastomosis. The difficulties experienced with suture line bleeding and early graft occlusion with a soft thrombus were essentially as already discussed in the section on carotid grafts.

Three dogs died and 9 were sacrificed. There was no evidence of infection or graft disruption or dilatation. There was no hematoma formation in any of the graft areas. Twelve of the grafts were patent (50 per cent) and 12 were occluded. A small mural thrombus was found on the wall of one of the patent grafts. Arteriography was used in some living animals to show the size and function of the grafted segments prior to sacrifice (Fig. 3).

FIG. 3. Roentgen demonstration of patency of bilateral femoral artery homografts.

ALCOHOL PRESERVED HOMOGRAFTS

Carotid grafts. Thirty-one alcohol preserved homografts were used to replace a resected section of carotid artery in dogs. The homografts had been stored in 70 per cent ethyl alcohol for periods ranging from 6 to 60 days (Table III). The grafts averaged 5.1 centimeters in length, and the average weight of the dogs was 9.3 kilograms.

The alcohol preserved grafts were inserted with the same technical ease experienced with the freeze-dried grafts. When the clamps were released, the difficulties with suture line bleeding and early thrombosis also were encountered and with approximately the same frequency as in the freeze-dried grafts.

Two dogs died and 14 were sacrificed. There was no infection or hematoma. Neither graft disruption nor dilatation were found. Twenty grafts were patent (64 per cent) and 11 were occluded. A small thrombus was found near the distal anastomosis of 1 of the patent grafts. The gross appearance of the alcohol preserved homografts at necropsy was identical to that of the freeze-dried

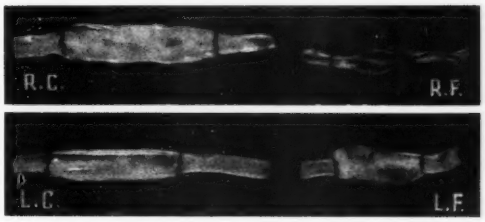


FIG. 4. Autopsy appearance of 4 alcohol preserved homografts 77 days after insertion. The graft to the right femoral artery was occluded with a thrombus and contracted. The other grafts were patent and normal in appearance.

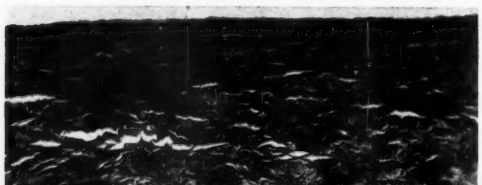


FIG. 5. Photomicrograph of an alcohol preserved homograft 77 days after placement showing evidence of smooth muscle hyalinization and vascular ingrowth from the host.

grafts (Fig. 4). A comparison of these short term results of carotid homografts as carotid artery replacements reveals, if anything, slight superiority of the alcohol preserved graft since of 26 freeze-dried grafts inserted 15 grafts (57 per cent) were found to be patent.

Microscopic study of several of the patent grafts showed evidence of smooth muscle hyalinization and some vascular ingrowth from the host (Fig. 5).

Femoral grafts. Thirty homografts, preserved from 6 to 60 days in 70 per cent ethyl alcohol, were used to replace femoral arteries bilaterally in 15 dogs (Table IV). The grafts averaged 4.8 centimeters in length. The technical difficulties of graft placement were the same as those found in the series of freeze-dried grafts to the femoral artery.

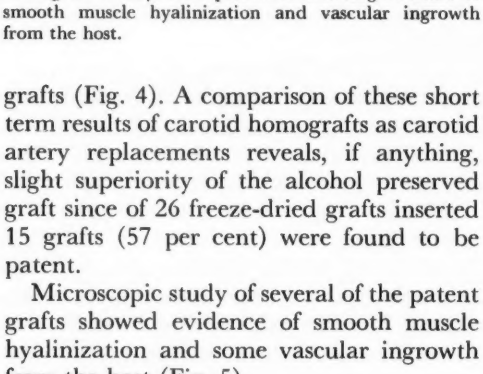


FIG. 6. Arteriogram illustrating the excellence of collateral circulation around the area of femoral homograft occlusion (arrows).

Two dogs died and 13 were sacrificed. There was no evidence of infection, aneurysm formation, or anastomotic disruption. However, a hematoma was discovered in the graft area at the level of the proximal anastomosis in 1 limb. This graft was occluded. Fourteen of the grafts were patent (47 per cent) and 16 were occluded. A small mural thrombus was found in 2 of the patent grafts. These findings are similar to those with freeze-dried carotid arteries for femoral artery replacement in which group 12 grafts (50 per cent) of 24 inserted were patent.

Because of the excellence of collateral circulation around both carotid and femoral arteries in dogs, the patency of these channels is not necessary for the survival of tissues distal to them. It was of interest that femoral artery pulsations were detected in a number of animals in which the graft was shown by arteriography or necropsy to be occluded. In some of the arteriograms, the excellence of the collateral circulation is clearly demonstrated (Fig. 6).

Impedance plethysmography was utilized frequently in the late evaluation of peripheral arterial circulation. However, this was found to be of little value in assessing graft patency because of the extensive collateral circulation which developed. Almost identical oscillations were encountered in limbs with occluded femoral homografts and in limbs with patent grafts (Fig. 7). It is probable that the use of impedance plethysmography would have been of more value in the early hours and days after operation.

DISCUSSION

The successful use of small artery grafts in experimental animals was described first by Höpfner in 1903. He used both fresh autografts and fresh homografts. Much of the initial work with small vessel transplantation was concerned with the histologic fate of the transplanted tissues.

The difficulty of maintaining patency of small artery grafts was emphasized in 1907

by Williamson and Mann. They found that 5 of 6 fresh carotid artery homografts were occluded when examined from 56 to 62 days after placement. Miller and his associates in 1951 studied the fate of small artery grafts in those dogs which survived hind leg transection and reimplantation experiments without gangrene for an initial critical 2 week period. Although the majority of the homografts, both fresh and preserved, remained patent after the initial 2 week period, approximately one-half of the homografts were found to have what the authors described as defects. Graft discoloration and roughening of the intimal walls were the principal defects encountered.

Twenty-four femoral artery homografts were inserted in dogs by Hiertonn in 1952. All but 5 of these grafts were stored in modified Tyrode's solution as described by Gross and his associates. Only 9 of the grafts (38 per cent) had remained patent up to 15 months on examination by aortography. In 1954, Creech and his associates reported that at examination all of 13 formalin preserved heterografts to dog carotid arteries had become occluded.

In this study, we were able to achieve an overall small artery graft patency of 55 per cent in 111 preserved homograft replacements of dog femoral and carotid arteries. In 54 femoral artery grafts, in which some disparity in size often existed, 48 per cent of the grafts were patent. The per cent of success rose to 61 in 57 carotid artery grafts. Carotid artery homografts were used for carotid replacement and the incidence of graft-host vessel disparity was somewhat less than in femoral replacement.

The need for improving the results of small artery grafting is apparent. Certain observations made during this investigation may be helpful. The frequent occurrence of thrombotic occlusion of the graft at the time of grafting suggests that the occlusion of most grafts occurs relatively soon after placement. It is possible that alterations in the technique of graft preparation and placement may lead to improved results. Some modifications in technique are currently under investigation. Included in these modifications are the addition of heparin to the isotonic saline solution used to reconstitute the grafts and the use of oblique end-to-end anastomoses.

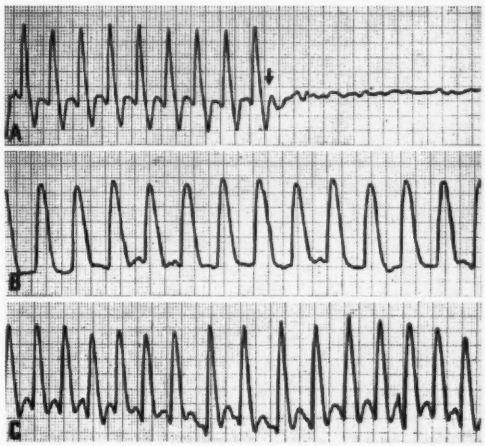


FIG. 7. Demonstration by impedance plethysmography: A, of the sudden reduction in peripheral oscillations produced by acute occlusion of the femoral artery (arrow), as compared with the excellent oscillations observed both, B, in a dog with a patent femoral homograft and, C, in the dog with the occluded femoral graft pictured in Figure 6.

It was of interest that the homografts preserved in 70 per cent alcohol proved to be at least equal to the freeze-dried grafts. In carotid artery replacements, 20 of 31 alcohol preserved homografts remained patent (64 per cent) as compared with 15 of 26 freeze-dried grafts (57 per cent).

Surprisingly, little effort has been directed toward determining the suitability of alcohol for the sterilization and preservation of arterial homografts. Its use in the preservation of dog carotid homografts was described by Nageotte and Sencert in 1919 and Hosomi in 1928. Paolucci and Tosatti in 1950 reported success in 4 of 5 dog aortic homografts preserved in pure alcohol. The grafts were reconstituted by a 2 hour washing in isotonic salt solution. The most thorough study of the use of alcohol preservation of arterial segments was published by Kimoto and his associates in 1954. They employed both pure

and 70 per cent alcohol in the preservation of aortic heterografts and homografts in dogs. The results with alcohol preserved aortic homografts compared favorably with those of viable preservation. Alcohol preservation considerably increased the likelihood of success in aortic heterografts. They also reported the use of arterial grafts preserved in alcohol in 11 humans. They concluded that 70 per cent alcohol preservation was superior to pure alcohol because of more effective sterilization and because the grafts more readily regained their softness when immersed in isotonic saline solution.

It should be pointed out that, while ethyl alcohol is an excellent bactericidal agent against the vegetative forms of bacterial life, it is relatively ineffectual against spore forms. This weak sporicidal action is shared by most chemical disinfectants.

The freeze-dried method of homograft preservation, introduced in 1951 by Marrangoni and Cecchini and Natellis and Visalli has been accorded great popularity in clinical use. Once lyophilization has been completed and the graft has been sealed in a nitrogen or carbon dioxide filled glass cylinder, its storage and subsequent preparation for use is most satisfactory. However, many institutions, where graft material is available and where its use might be required, do not have the equipment, financial support, and "know-how" necessary to set up a freeze-dried blood vessel bank. If no more than a sterile container and some 70 per cent ethyl alcohol is required for satisfactory preservation, the scope of homograft procurement and use may be greatly expanded.

SUMMARY

1. The experience with 111 freeze-dried and alcohol preserved arterial homografts used to replace small caliber arteries in dogs is reported.

2. Dog carotid artery was utilized as the homograft material in all replacements, for both femoral and carotid arteries. The grafts averaged 5 centimeters in length. Anticoagulants were not used.

3. Sixty-one of the 111 grafts (55 per cent) remained patent and functioned satisfactorily. A 61 per cent patency was achieved in 57 carotid artery replacements as compared with a patency of 48 per cent in 54 femoral grafts.

4. Some problems of a general nature pertaining to the placement of small caliber arterial grafts, especially the hazard of early thrombosis, are discussed.

5. Small caliber arterial homografts preserved in 70 per cent ethyl alcohol were found to be at least as satisfactory as the freeze-dried grafts.

6. The potential value of the use of alcohol in increasing the scope of arterial homograft procurement and use is emphasized.

REFERENCES

1. Creech, O., Jr., DeBakey, M. E., Self, M., and Halpert, B. The fate of heterologous arterial grafts. Surgery, 1954, 36: 431.
2. Gross, R. E., Bill, A. H., and Peirce, E. C. Methods for preservation and transplantation of arterial grafts. Surg. Gyn. Obst., 1949, 88: 689.
3. Hiertonn, T. Arterial homografts. Acta orthop. scand., 1952, Suppl. X.
4. Höpfner, E. Ueber Gefaessnaht, Gefaesstransplantationen und Replantation von amputierten Extremitaeten. Arch. klin. Chir., 1903, 70: 417.
5. Hosomi, K. Experimentelle und klinische Untersuchungen ueber die freie Transplantation toter (in Alkohol oder Formalin konservierter) Gewebe. Deut. Zschr. Chir., 1928, 209: 14.
6. Kimoto, S., Sugie, S., and Tsunoda, M. Experimental and clinical studies on arterial homo- and hetero-grafts preserved in alcohol. Arch. Surg., 1954, 69: 549.
7. Marrangoni, A. G., and Cecchini, L. P. Homotransplantation of arterial segments preserved by the freeze-drying method. Ann. Surg., 1951, 134: 977.
8. Miller, H. H., Callow, A. D., Welch, C. S., and MacMahon, H. E. The fate of arterial grafts in small arteries. Surg. Gyn. Obst., 1951, 92: 581.
9. Nageotte, J., and Sencert, C. Sur les phenomenes biologiques mis en evidence par les greffes des arteres mortes. C. rend Soc. mém. biol., 1919, 82: 45.
10. Natellis, F., and Visalli, F. Trapianti di arterie trattate con la liofilizzazione, Arch. ital. chir., 1951, 74: 327.
11. Paolucci, R., and Tosatti, E. Homografts of aorta preserved in alcohol. J. Internat. Coll. Surgeons, 1950, 14: 257.
12. Williamson, C. S., and Mann, F. C. Functional survival of autogenous and homogenous transplants of blood vessels. Arch. Surg., 1947, 54: 529.

CLINICAL SIGNIFICANCE OF CHANGES IN COMMON DUCT BILE RESULTING FROM A NEW SYNTHETIC CHOLERETIC

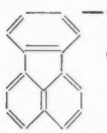
JOHN M. McGOWAN, M.D., B.S., M.S.(Surg.), F.A.C.S., F.R.C.S., Quincy, Massachusetts

A NEW SYNTHETIC CHOLERETIC AGENT, designated as SC 1674, and subsequently named "anchol," was given to 34 patients with biliary disease. A study was made of these cases over a 3 year period. The changes brought about in the physical properties of bile after the administration of anchol indicate that this drug should be useful in the treatment of biliary disease. The results of a clinical study of the effect upon symptoms of biliary disease are also promising.

The changes in the character of bile were so different from those produced by other choleretic agents, and so striking, that a report of these changes seems justifiable. This article is concerned mainly with a report of results of a study of the bile in 13 patients who had T-tube drainage of the common bile duct for long periods after operation.

PHARMACOLOGIC DATA

A synthetic choleretic substance designated as SC 1674 was made available for study in May of 1952. It is a stable, golden yellow, crystalline solid, which is insoluble in water and acids but moderately soluble in organic solvents and in alkaline media. The descriptive formula of SC 1674 is Y-oxy-Y fluoranthenebutyric acid and its structural formula may be represented as follows:



The oral medial lethal dose of SC 1674 in mice is 1,160 milligrams and in rats 2,500 milligrams per kilogram of body weight. These ranges of toxicity indicate a high index of therapeutic safety.

After the first few patients had received this preparation, its usefulness was so obvious that it was prescribed routinely for all patients operated upon for gallbladder disease in whom it was necessary to place a T tube in the common bile duct for prolonged biliary drainage, and also for patients suffering from symptoms of biliary disease but not requiring surgery.

Increase in the volume of bile was looked for at first but did not appear to be great, and therefore, intensive studies of the effect on volume did not seem to be indicated. More recently, however, it was noted that a progressive increase in the flow of bile did occur. The changes in the quality of the bile, noted from the very first, were striking and the potentialities for good attracted attention.

The changes noted in the bile will be discussed under the following headings: (1) color, (2) viscosity, (3) degree of sediment, (4) bacterial content, (5) detergent action, and (6) action on parenchymal liver cells.

Color. In every case of T-tube bile studied, there was a color change. The bile changed from its original color, which ranged from a clear, canary yellow bile to a muddy, thin bile containing precipitates. In every instance, regardless of the original color, the bile changed to a brilliant deep green, and the sediment disappeared.

Viscosity. Viscosity studies are planned for the future. However, the general impression, upon shaking the preparation in a bottle, was that the viscosity was considerably

From the Department of Surgery, Quincy City Hospital, Quincy, Massachusetts.

lower. Clinically, this appeared to be true. Two patients, in particular, who had partial obstruction of the biliary tract from extrinsic pressure appeared to be benefited by anchol. In neither of these patients would sufficient bile pass through the common duct to keep the patient free from jaundice. In one patient, it was necessary for the indwelling T tube to be open at all times. The other patient had jaundice with an icteric index of 50. In both these patients, the bile flowed readily through the common duct into the duodenum after the administration of SC 1674, so that in a period of several weeks the condition of both had returned to normal.

Degree of sediment. The sediment disappeared in approximately 5 to 10 days after the administration of SC 1674 in all 13 cases of T-tube bile studied. A constant characteristic was the fact that the precipitated bilirubin and other sediment was put into solution by the preparation. The bilirubin noted on centrifuging and on microscopic examination disappeared. This disappearance of sediment was progressive from day to day. By the fifth to tenth day, all sediment had disappeared in most cases (Fig. 1). On removal of the T tube, in each case, it was noted that the tube was unusually clean, whereas usually the T tube is covered with sediment.

Freezing point studies should be done to determine the amount of solutes in the bile. In 1 case, specimens, including 1 taken prior to the administration of SC 1674 and 5 afterward, were exposed to winter temperatures, well below freezing. The specimen taken prior to SC 1674 was frozen solid in the test tube. None of the other specimens was frozen.

Bacterial content. Specimens taken before SC 1674 was given developed a putrid odor at room temperature within 24 to 48 hours. After the administration of SC 1674, many specimens had no odor, and motile bacteria were reduced in number or were absent.

Detergent action. There was a definite detergent action noted in all cases. The bile taken from specimens prior to the administration of the drug showed a certain amount of foam upon being shaken. The amount of foam after the use of SC 1674 was much greater in height (Fig. 2). The bubbles were much more regular in consistency, and the froth lasted for a much longer period of time.

Surface tension studies were made in a few cases at the Massachusetts Institute of Technology. No appreciable change was noted. However, examination of those cases in which surface tension studies had been made, revealed that these specimens had been taken from patients with liver damage who had been receiving the preparation for only a short time. If the drug were to be given for a longer period of time to patients with better liver function, a more accurate evaluation of surface tension changes could be made.

Action on parenchymal liver cells. It would be safe to say that this preparation improves liver function. It is a known physiologic fact that green bile does not come from the common duct under normal and average circumstances. It is only when the liver is in unusually good condition and well supplied with glycogen that green bile comes from the common duct directly. In every instance, in all 13 cases of T-tube drainage which were studied, the bile turned green with consistency after the administration of SC 1674.

METHOD OF STUDY

Patients were divided into four classes:

1. Those upon whom cholecystectomy had been performed and a McGowan-Keeley T tube placed in the common duct for prolonged biliary drainage. Thirteen cases were studied.

2. Patients who had previously been operated upon without biliary drainage who subsequently developed biliary symptoms. Five cases were studied.

3. Patients who had been previously operated upon for cholecystitis but whose common duct was not drained, and who re-

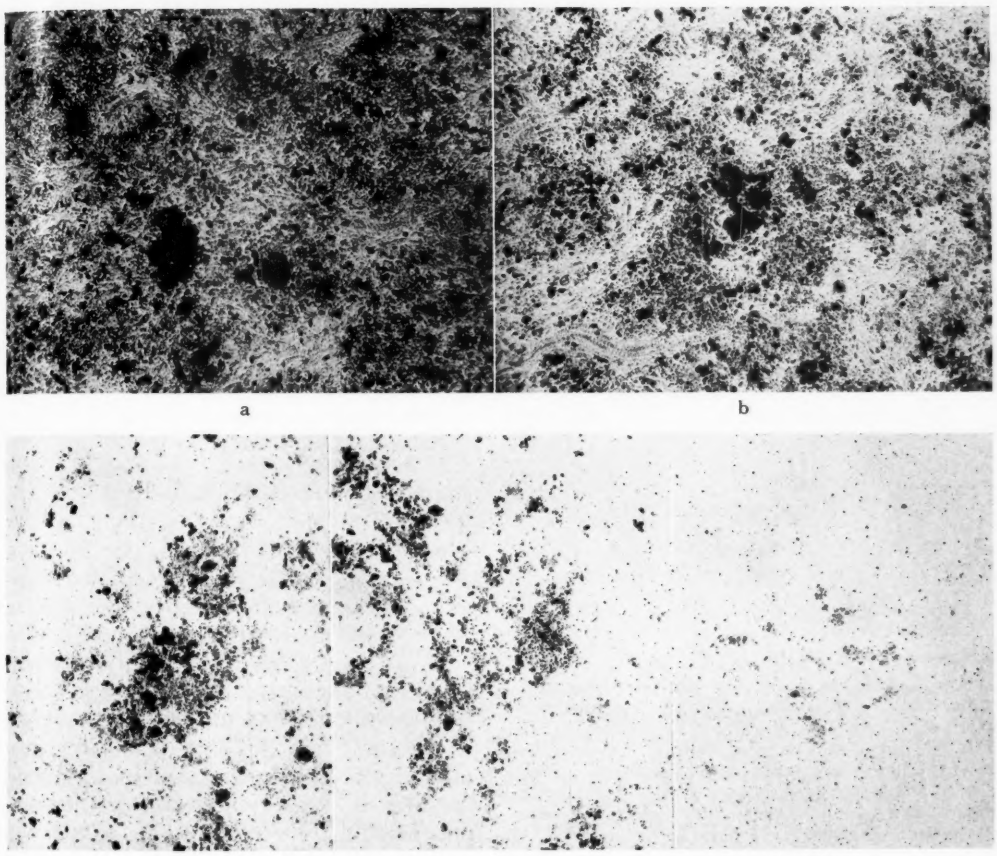


FIG. 1. Photomicrographs showing the sediment from centrifuged bile taken from patient with T-tube drainage following cholecystectomy. a, Before administration of SC 1674. b, c, d, and e, Taken daily following administration of SC 1674. Note the gradual disappearance of sediment which consisted of inspissated bilirubin, crystals, and motile bacteria.

quired subsequent operation upon the common duct with T-tube drainage. Two cases were studied.

4. Patients with symptoms simulating cholecystitis—some with stones proved by x-ray examination—who were treated medically with SC 1674. Fourteen cases were studied.

A dosage schedule of one 250 milligram tablet 4 times daily appeared adequate. Two tablets (500 mgm.) 3 times daily were given to a small number of patients without any noticeable difference in reaction or results.

From the postcholecystectomy patients who had a T-tube in the common bile duct; bile was collected for a 3 hour period at the same time each day, from 9:00 a.m. until 12 noon. A 3 hour specimen was taken prior to the administration of the drug and daily thereafter. Studies were begun after the fifteenth postoperative day, usually on the twenty-first day. The T-tube bile was studied grossly for color change, sediment, odor, and detergent action. Microscopically, the sediment was examined for pus, bacteria, bilirubin, and crystals. In a few cases, sur-

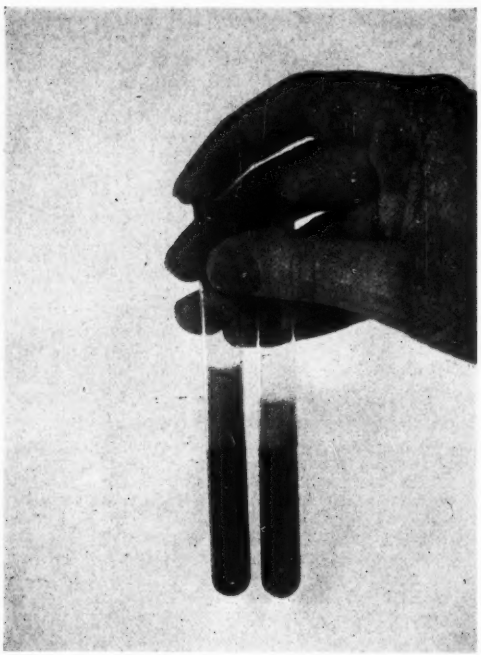


FIG. 2. The color change and improved detergent action of SC 1674 are shown. The tube on the right was taken from a patient after gallbladder operation and represents T-tube bile. Note the light color of the bile and the height of foam after shaking. This bile was canary yellow with considerable sediment and opacity. The bile on the left is darker in color with a higher foam, representing more even bubbles. This bile was taken from the patient 1 day after SC 1674 was administered. It has more color and has less sediment. The inference in observing these specimens is that SC 1674 improves the function of bile to keep precipitates in solution and improves its detergent action.

face tension determinations were made. These patients were also studied for evidence of side reactions.

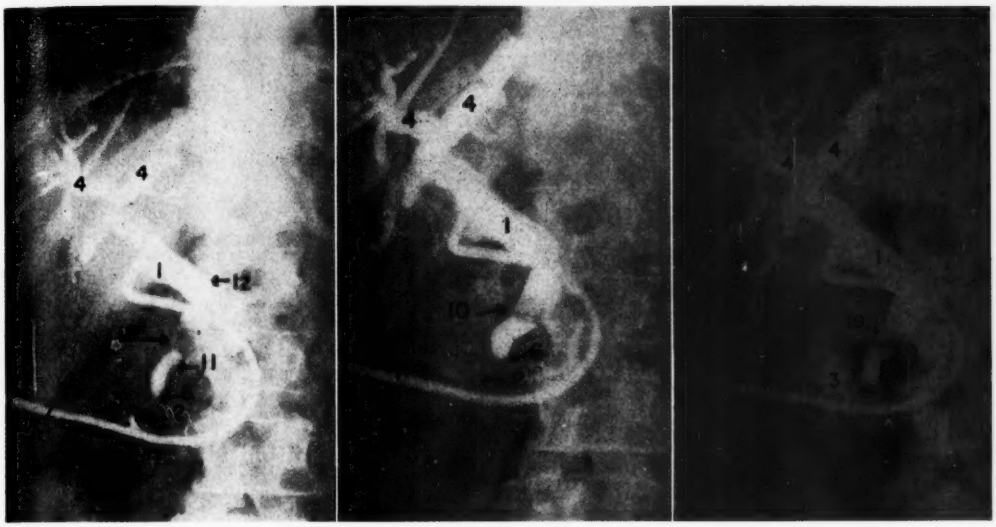
In order to study evidence of residual biliary infection intrabiliary pressure studies were made on the twenty-first postoperative day, and the resting intrabiliary pressure was determined to measure the degree of residual infection in the biliary tract. Postoperative cholangiograms were done routinely. Thirteen cases were studied. Follow-up studies were made on the patients for periods up to 3 years in order to determine the general state of health and evidence of biliary symptoms.

RESULTS

The bile study indicated a color change from yellow to green in 24 hours in every case. In some cases this color change was noted on several occasions with repeated courses of the agent. The color can best be described as a deep, brilliant green.

Sediment was noted microscopically in every case studied with T-tube drainage. Microscopically, sediment consisted chiefly of inspissated bilirubin, epithelial cells, crystals, and, on occasion, pus cells. Sediment was measured by centrifuging as well as microscopically. After centrifuging the specimen, the amount of sediment in the bottom of the centrifuge tube was measured and recorded in millimeters. The sediment was examined microscopically. In every instance, the sediment disappeared with the administration of SC 1674 within 5 to 10 days. This disappearance of sediment indicated that this preparation enabled the bile to keep sediment in solution (Fig. 1). The value of this property of keeping sediment in solution is obvious. Removal of sediment by solution is the function of the normal bile in healthy biliary systems. In the presence of biliary tract infections, the bacteria split the bile acids into various chemical components. The bile then loses its capacity to keep the various constituents in solution, and precipitation and stones result. In patients with T-tube biliary drainage, precipitation of bilirubin and eventual plugging of the T tube have long been recognized as a handicap to therapy.

The ability of bile to dissolve sediment appears to be promptly restored by SC 1674 in the patients with biliary disease who require T-tube drainage. This detergent action should prove beneficial in washing bacteria from the bile ducts. Removal of sediment should result in a free flow of bile and improved biliary drainage. It was noted with consistency that the T tube, when it was removed from the bile duct, after several weeks or months indwelling, was free from sediment or encrustations in patients receiving SC 1674 at the time of the tube removal.



a b c

FIG. 3. Cholangiograms of a patient following cholecystectomy for obstructive jaundice, in whom a McGowan-Keeley T tube was placed into the common bile duct at the time of operation. The numbering on the x-ray film is a standard used by the author. Each number represents structures as follow: *1*, common duct; *2*, point at which the bile duct enters the duodenal lumen (ampulla of Vater), *3*, contrast media in the duodenum, *4*, hepatic ducts and finer radicles of the biliary tree, *5*, pancreatic ducts (not seen on this film), *6*, point at which the common duct begins to penetrate the musculature within the duodenal wall (sphincter of Oddi), *7*, T tube, *8*, cystic duct (not present), *9*, indwelling stomach tube (not present), *10*, extrinsic pressure—lymph node, *11*, common duct —distal to extrinsic pressure, and *12*, common duct proximal to extrinsic obstruction. a, Note the obstruction just proximal to the sphincter of the common duct, note the dilation above the point of obstruction and the narrowing below. This obstruction might be interpreted as a stone in the bile duct, roentgenologically, however, at the operating table, it was demonstrated to be extrinsic pressure from an inflamed lymph node. b, Same as "a" taken 10 minutes after administration of morphine sulfate, subcutaneously, in a dose of 10 milligrams (⅙ gr.). Note the spasm at *6*, the point at which the common duct enters the duodenal wall. c, The same as "a" and "b" following inhalation of amyl nitrate. Note the relaxation of duodenal musculature at *6* and the free flow of the media into the duodenum.

This condition is quite the opposite from what has been noted in the past. It has long been a known fact among doctors doing biliary surgery that tubes become covered and often plugged with orange colored sediment of bilirubin after a sojourn in the common duct and that a prosthesis, such as a rubber or metal tube, put into the duct to replace a destroyed portion of the duct invariably becomes plugged and reoperation is required. From this study, it is safe to conclude that such patients could be benefited indefinitely by the administration of SC 1674.

Detailed, scientific studies of viscosity are now under way. However, the bile appeared to have a reduced viscosity after the administration of SC 1674 which fact was noted on shaking and pouring of the specimens. In 2 cases of proved partial biliary obstruction, as a result of extrinsic pressure on the common duct, administration of the preparation enabled the bile to flow freely through a common duct with reduced lumen. Neither patient showed any improvement after several months. With the administration of SC 1674, both patients improved progressively to a cure.

CASE 1. The first case was that of a white female, 62 years old, with extrinsic pressure on the common duct from a lymph node, demonstrated at operation.

This obstruction had been sufficient to produce jaundice with an icteric index of 50 (Fig. 3a, b, and c). Three months postoperatively, there was still enough pressure from the lymph node to produce a resting intrabiliary pressure of 200 millimeters of water above the ensiform (normal 30 mm. water or less). This degree of obstruction is demonstrated on cholangiogram (Fig. 3a, b, and c). There was residual infection in the radicles of the biliary tree so that at 300 millimeters of water the patient suffered biliary pain. The degree of obstruction had become more marked 2 months after operation (Fig. 4a, b, and c). Following the administration of SC 1674, she was able to tolerate increasing periods of T-tube clamping, so that after 3 weeks the tube could be clamped off at all times. The biliary dynamics gradually returned to normal, so that after 6 straight weeks of medication with SC 1674 the resting intrabiliary pressure was down to 50, from an original 200 (normal, 30), and the perfusion pain pressure was up to 500, from an original 300 (normal, 550 or more).

The T tube was removed 5 months after operation for obstructive jaundice due to extrinsic pressure. Obstruction was due to a lymph node not removed at the time of surgery, because of fear of endangering the circulation to the common duct with a resulting fibrosis. After 4 months of T-tube drainage there was still resistance to the flow of bile to the level of 200 millimeters of water. After 6 weeks of SC 1674, the resting pressure was down to 50 millimeters of water. The T tube was removed, and 2 years afterward the patient was still symptom-free.

The wonderful result with this case is attributed to several factors: (1) reduction of sediment and infection in the bile, resulting in lowering surface tension and viscosity; (2) a free flow of bile through a reduced lumen; and (3) improvement in general health because of a restoration of bile to the gastrointestinal tract, resulting in a resolution of lymphadenitis in the lymph node which had been producing the extrinsic pressure. (The cholangiogram, Fig. 3a, b, and c, indicates partial obstruction. The cholangiogram taken later, Fig. 4a, b, and c, shows increased obstruction. Since jaundice existed just prior to the studies noted in Fig. 3a, b, and c, jaundice certainly would have been present later, except for a T tube.)

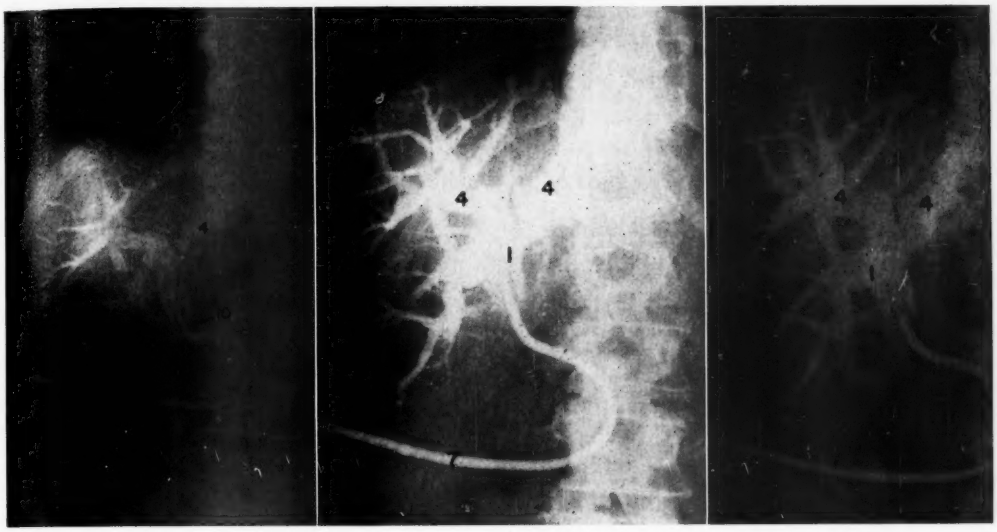
CASE 2. The second case was that of a diabetic male, 67 years old, who suffered acute cholecystitis accompanied by obstructive jaundice, icteric index, 60. At operation, the gallbladder was so thick-walled and edematous and so adherent to the surrounding structures, that it was impossible to identify the common duct and unsafe to try to explore it. The gallbladder could not be removed, so it was drained with a mushroom catheter. Postoperatively, the patient improved at first, but soon the bile ceased to flow from the gallbladder tube, and jaundice became more intensive. Symptoms of impairment of liver function appeared. The icteric index rose to 81, and was reduced to 50 by duodenal drainage. The patient was not fit for reoperation. A diagnosis of the inflamed gallbladder was made, with secondary biliary obstruction. The patient was sent home from the hospital on SC 1674, 250 milligrams, 4 times a day. He was continued on SC 1674 for 2 months, at the end of which time he was entirely symptom-free, and all chemistry studies indicated the absence of icteric and the return of normal liver function. Follow-up examination 6 months later found the patient entirely symptom-free.

CLINICAL STUDIES

Side reaction. In all 34 cases studied, there were no untoward side reactions to the drug. A considerable number of patients stated that the bowels moved more freely, and the stools were a darker shade, toward a green. In constipated patients, the change in bowel function was considered beneficial by the patient. There was no evidence of gastric irritation by the drug.

Biliary dynamics. Each case was studied periodically with reference to intrabiliary pressure. Studies were made of the resting intrabiliary pressure as an index of the patency of the lower end of the bile duct. The normal resting intrabiliary pressure is 30 millimeters of water above the ensiform. Increased pressure is due to ampulla edema, spasm of the sphincter of Oddi, a missed intrabiliary stone, or pancreatic edema. The perfusion pain pressure is a measure of residual biliary infection. The normal is up to 550 millimeters of water.

When infection is present in the intrabiliary tract, one would expect more speedy recovery in patients with T-tube drainage if a good bile detergent were used. Collectively, it was difficult to establish a relation between biliary dynamics and SC 1674. However, in individual cases, results were more striking. The cases referred to were the more stubborn infections which were slow to improve with T-tube drainage. The re-



a b c

FIG. 4. Same as Figure 3, two months later. The signs of obstruction had become progressively worse. When these films were taken the patient could not clamp the T-tube off without suffering pain. Roentgenograms were taken serially under conditions as described in Figure 3. a, Resting; b, after morphine; c, after amyl nitrate. Note the obstruction now appears to be complete, roentgenologically. By biliary dynamic studies, however, bile could be perfused through the lower end of the duct, but under such great pressures as to be intolerable to the patient and to prevent liver function. This patient, therefore, would have been in a state of painful jaundice, obstructive in nature, except for T-tube drainage. Following SC 1674, given continuously, the T tube was able to be clamped off for increasing intervals, so that 3 weeks after the preparation had been given continuously, the T tube could be clamped off 24 hours without pain.

sidual biliary infection subsided gradually, with consistency, following the administration of SC 1674, although results were more spectacular when injection of streptomycin into the T tube was used in conjunction with SC 1674. One observation worthy of mention is that prolonged continued use of the drug for 3 or more weeks was much more definite and lasting in its effects than repeated periods of 6 days each.

Follow-up results. All patients were followed for from 6 months to 3 years. The results were all excellent. Very few of these patients had even mild residual biliary symptoms.

Change in quantity of bile flow. There was a definite increase in the flow of bile in 2 cases studied. Other cases studied did not show any appreciable change. However, it was noted in the study that the increase in the volume of bile is progressive and was more noticeable after 5 days. It is probable that if cases were studied over a longer period of time, we would probably find a greater increase.

In the beginning of this study, SC 1674 was given for short periods of 5 days each. More recently, it has been found that the effects are additive, improving from day to day, and that longer periods of study for up to 3 weeks would more accurately evaluate the benefits of this preparation. As previously stated, the sediment disappears progressively from the bile and the bile flows more freely into the duodenum. Volume increase determinations would be difficult because, after the administration of SC 1674, more bile flows into the duodenum as a result of the detergent and less comes out of the tube.

SUMMARY

1. SC 1674 was administered to 34 patients. No untoward reaction was noted in any of the patients studied. In 13 of the patients who had a T-tube in the bile duct, studies were made of the liver bile and a report on the basis of these 13 cases is presented.

2. After the administration of SC 1674, the bile changed color consistently, from yellow to a brilliant green. The quality of the bile changed, sediment, when present, progressively disappeared until between the fifth and tenth days the bile was entirely free of sediment. Any sediment present before the treatment disappeared, and the bile became clear and a brilliant green in color. The freezing point was lowered considerably, a fact substantiating the ability of the bile to put sediment into solution. There is some evidence to indicate that SC 1674 acts as a biliary detergent.

3. The T tubes removed during the time that the patients were being given preparation were extremely clean and free from sediment, contrary to conditions noted otherwise, when the T tubes are covered with inspissated bilirubin, another indication of the detergent action of SC 1674.

4. These studies demonstrate that SC 1674 changed the characteristic of bile in such a manner as to indicate the usefulness of the preparation in biliary disease. It has been found beneficial in eliminating residual biliary infection in patients with T-tube drainage following surgery.

5. Use of the drug should be beneficial under the following circumstances: (a) in all cases after biliary surgery to prevent the so-called postcholecystectomy syndrome; (b) in treating without surgery some cases simulating cholecystitis. (The benefit here, however, as one would expect, is variable because many patients with biliary infection have some mechanical defect requiring surgical correction.) (c) Since the bile is changed from yellow to green in a short time, and since green bile coming directly from the common bile duct is usually associated with an excellent liver function with adequate glycogen stores, the possibility of SC 1674 acting beneficially, upon the parenchymal liver cells, must be considered.

6. The results obtained in 13 patients with T-tube drainage are reported. No untoward results were noted in any of the 34 patients receiving SC 1674. These patients will be the subject of a future report.

CANCER OF THE THYROID GLAND

DONALD E. ROSS, M.D., F.A.C.S., Los Angeles, California

IT MUST BE EMPHASIZED that any tumor which may invade locally and spread by metastasis to kill the patient must be regarded as a serious cancer. It should be treated vigorously with all the means at our command.

The present material consists of 40 cases of proved cancer and represents 1,000 thyroidectomies performed between 1945 and 1955, or an incidence of cancer in my series of 4 per cent of all thyroid cases operated upon. It is hoped that a review of these cases may be helpful in establishing the necessity for radical surgery.

According to Sokal, cancer of the thyroid gland is responsible for 1,000 deaths in the United States annually and accounts for 0.56 per cent of all cancer and 0.41 per cent of deaths from cancer. In Cohen and Moore's series of 101 patients with thyroid cancer, 47 per cent survived 3 years, 34 per cent survived 5 years, 24 per cent survived 10 years, and only 14 per cent survived 15 years. Yet there is a persistent tendency to minimize its malignancy and to curtail the scope of surgery. Fortunately, many still believe in the traditional methods of removing cancer, together with the lymph drainage, in a block dissection. McClintock, for example, reminds that the lymph drainage extends into the upper mediastinum and suggests enlarging the operation by splitting the sternum in order to enable removal of these nodes, together with a block dissection of the neck. I thoroughly agree that adequate surgery should be performed. A suprahyoid dissection is always done as well, since several patients in the present series were found to have positive nodes extending as far as the base of the skull.

Cancer of the thyroid gland may occur at any age. Of the 40 patients in this series whose average age was 41 years, 7 (17.5 per cent) were under 20 years of age. Thyroid enlargements in this age group are particularly likely to be malignant. Of 14 children operated upon, 7 had malignant tumors. One boy, 5 years of age, had widespread metastases to the lungs which fortunately responded to radioactive iodine, and he is well and free from disease 6 years later. Twenty-six (65 per cent) of the patients were females.

Table I shows 8 patients who were clinically toxic and yet had carcinoma of the thyroid gland. The theory that toxicity precludes the presence of cancer is therefore not entirely true. Cancer is found in a much higher percentage of these cases than is usually quoted.

Table II shows that of 40 patients 7 have died. Four had rapidly growing invasive types of tumors and their condition was hopeless from the start. In all these cases operation is performed in the belief that palliative surgery may be very helpful. Even a tracheostomy provides relief for a considerable period of time. One wonders if some of these patients should be operated upon with hope of cure. One patient in the series with a large anaplastic type of tumor is well after 5 years. One patient succumbed to an attack of coronary heart disease. At autopsy, there was positive cancer metastasis in the mediastinum. The last death (Case 40) is most instructive and interesting. Two years ago this patient was operated upon by an excellent thyroid surgeon who performed a total thyroidectomy, leaving a small amount of tissue on one side. No follow-up gland dissection was performed. Neither were there any radioactive iodine studies. One year later, a pneumonectomy was performed in the mistaken idea that a primary pulmonary cancer existed. In reality, metastatic carcinoma from the thyroid was present. One year after this he was

TABLE I.—MALIGNANCY OCCURRING IN CLINICALLY TOXIC GOITER

Case No.	*Preoperative history*
4.....	After medication (Lugol's), the basal metabolism came down to normal
7.....	Operated upon in stages from what appeared to be extreme toxicity
12.....	Had all the other symptoms. Weakness, tachycardia, tremor. Under iodine treatment, came down to plus 2, minus 2
17.....	27.3 per cent radioactive iodine uptake—upper range of normal. She was a thin, nervous child with rapid heart
19.....	Under preparation with Lugol's solution the basal metabolism receded to plus 1 preoperatively
27.....	Was treated by iodine and tapazole. Basal metabolism rate came down to normal before surgery. It was minus 16 three years ago. Had all the typical symptoms of hyperthyroidism now
29.....	Exophthalmic goiter. All the typical symptoms of toxicity. Prepared with Lugol's solution
31.....	Was said to be toxic. Was very nervous, thin, and had tachycardia

operated upon for spinal cord tumor which also proved to be metastatic cancer from the thyroid. A few months later he presented himself to us with nodular masses of carcinoma in the neck. These were invading the larynx and esophagus as well as pressing on these areas. Here, then, is an example of cancer of the thyroid gland which did not remain dormant and innocuous. The metastases in the neck which were probably present at the time of the original surgery most assuredly grew locally in the neck and undoubtedly metastasis took place to the lungs, spinal cord, and other places as was shown at autopsy. One cannot but comment that it was a pity that more adequate surgery (block resection of the neck) had not been performed and followed up with radioactive iodine studies, including thyrograms. It may be seen in the thyrograms in the present study (Fig. 8) that the uptake is rather good. I fully expect many more such cases will be reported before long.

Cancer of the thyroid has often been divided into two classes. The first consists of those fulminating types, often large, round-celled or anaplastic, from which it is thought the patient must die in spite of anything that can be done. The other types offer more hope for cure. It is strange that the attitude has gradually and persistently been to regard the latter more and more lightly and to treat them as if they were relatively benign. I am positive this is erroneous thinking and can lead only to disaster in the form of recurrent disease.

Table III shows the various types of malignant tumors in the series. One patient who had the solid anaplastic type of cancer is still alive and well after 5 years. It may be seen that the great majority of cancers are of the papillary variety or a combination of this type with the alveolar. X-ray therapy is of little or no value in the treatment of such lesions of the thyroid gland or their metastases. Nor is the use of radioactive iodine justifiable as the sole therapeutic agent, since, as Egnark and his associates have shown, very few of these tumors or their metastases take up sufficient iodine. The only hope, therefore, is adequate surgery which means a minimum procedure consisting of a complete thyroidectomy with block dissection of the same side of the neck.

Table IV illustrates the location of the cancer in relation to the lobes. Both lobes were affected in 11 of 40 patients in this series, which is 27.5 per cent. In 7.5 per cent, multiple foci in one or both lobes were found. Lesions which occurred in the isthmus often invaded the lateral lobes and represented 25 per cent of the total number of cases in the series. It is apparent that total thyroidectomy should be performed in all cases of malignancy. Leaving a small piece of thyroid on the less affected side is to be condemned as unnecessary and dangerous, and this procedure does not fit into our follow-up methods.

Complete thyroidectomy is advisable when operating for multiple nodular goiter. It is unwise to leave adenomatous tissue because of possible recurrence. Indeed, in at least 2 cases in the series the recurrence proved to be malignant. Perfect replacement is quite possible with thyroid extract administration, and, in skilled hands, surgery is not appreciably more dangerous to the recurrent nerve. Whenever previous surgery has been performed, the vocal cords should always be examined preoperatively as a pre-

TABLE II.—DEATHS

Case No.	Comment	Date of surgery	Date of death
3.....	Advanced carcinoma in both lobes and in neck glands. Cachectic when first seen. Local infiltration. Died 7 months later of cancer. Hopeless case	4–17–39	11–18–39
20.....	Cancer infiltrating larynx and pharynx and causing dyspnea. Cardiac arrest. Chest opened and heart massaged. Lived 12 hours. Hopeless case	9–23–48	9–24–48
18.....	Hard nodular goiter for 10 years. Delayed surgery until she had extreme dysphagia. Invasion of trachea and esophagus. Hopeless case	9–8–42	10–8–42
9.....	Aged 73. Massive tumor in neck with large metastasis to sternum. Given postoperative radioactive iodine. Hopeless case	10–4–50	11–15–50
10.....	Rather advanced case. Hard nodular goiter. Both lobes cancerous. Died of coronary heart attack, but metastasis to superior mediastinum was believed present at death	3–31–48	6–1–50
19.....	Died of new cancer, i.e., cancer of bowel with new metastases to liver. No sign of recurrence in thyroid	4–27–42	11–25–45
40.....	Operated upon elsewhere (see Table VII). Included here to illustrate a case in which further surgery had been deemed unnecessary. The recurrence and death demonstrate how wrong this doctrine can be		

Three other cases were not included in our series. The pathology was squamous carcinoma involving the thyroid gland, esophagus, and larynx and other soft tissues. It could not be definitely stated that these arose in the thyroid gland, although no other site could be found at autopsy.

TABLE III.—PATHOLOGY

Type of tumor	No. of cases	Per cent
Adenocarcinoma	11	27.5
Papillary	17	42.5
Mixed alveolar and papillary	4	10.0
Hürthle cell	5	12.5
Solid anaplastic	1	2.5
Spindle and polyhedral	2	5.0
Total	40	100.0

Three cases of squamous cell cancer were not included in the series, as they could not be proved to originate in the thyroid gland.

TABLE IV.—POSITION OF THE TUMOR IN RELATION TO THE LOBES

Position	No. of cases	Per cent
One lobe only	26	60.5
Both lobes contained cancer areas	11	27.5
Isthmus chiefly	10	25
Single nodules only	18	40.5
Multiple foci in same lobe	3	7.5
Diffuse infiltration of both lobes and isthmus	4	15

TABLE V.—TYPE OF SURGERY PERFORMED

Case No.	Surgery	No. of cases	Per cent
21, 22, 31	Lobectomy only	3	7.5
26, 28	Isthmus and portion of each lobe	2	5
1, 4, 6, 7, 8, 9, 12, 13, 19, 33, 40	Total thyroidectomy only	11	27.5
2, 3, 18, 20, 24, 27, 29, 30 34, 35, 36, 38	Total thyroidectomy and block dissection on one side only	12	30
5, 10, 11, 14, 15, 16, 17, 23, 25, 32, 37, 39	Total thyroidectomy and block dissection on both sides	12	30
		40	100.0

cautionary measure to see if there is any resultant paralysis.

Of the 11 patients whose surgery consisted of complete thyroidectomy only (Table V), 2 had advanced tumors and were considered to be hopeless cases. In these no further measures were taken. One patient, 5 years of age, had widespread metastases to both lungs, and he received radioactive iodine therapy. Six years later, he is perfectly well and shows no evidence of metastasis. One child, 8 years of age, had diffuse carcinoma of both lobes and isthmus. She is well and living after 5 years.

Table V shows that complete thyroidectomy was performed in 87.5 per cent of the cases. It is now our mature judgment that this, plus block dissection on the same side, should be the minimum operation. It is my conviction that adenomas, whether encapsulated or not, do have lymphatics and can metastasize. Two of my patients (Cases 24 and 29) had well encapsulated single nodules, and, in Case 24, a block resection of the neck on the same side revealed widespread metastases to the glands. The other patient (Case 29) had a single, well encapsulated nodule in the center of a hyperplastic goiter. Complete thyroidectomy only was performed, and following surgery x-ray therapy was initiated. While this was being given, hard lymph nodes popped out on both sides which were proved positive metastatic cancer by subsequent block resection on both sides of the neck. That this patient is well after 10 years attests to the value of the adequate resection.

TABLE VI.—POSTOPERATIVE FOLLOW-UP

Duration	*No.*	*Per cent*
Under 5 years	15	37.5
Over 5 years	12	30
Over 10 years	6	15
Deceased	7	17.5
5 cases hopeless, 1 coronary heart attack presumed to have mediastinal metastases. No thyroid recurrence at autopsy		
1 died after 3½ years of cancer of the bowel (new cancer)		
1 died of recurrent cancer of the thyroid		
	40	100.0

The incidence of lymph node metastases in those cases in which bilateral block dissections of the neck were performed was as follows: 4 cases of positive glands in one side only; 6 of positive glands in both sides; and 3 cases in which there were no positive glands on either side. In the 12 cases in which unilateral neck dissections were performed, the incidence was 7 cases of positive nodes and 5 of negative. Since positive metastases were found in 17 of the 24 dissections (71 per cent), it seems evident that block dissections of the neck are absolutely necessary. It is emphasized that "local resections" are not sufficient, since in several cases positive nodes were found along the jugular vein right up to the base of the skull. These can only be eradicated by adequate wide resection.

TABLE VII.—PREVIOUS SURGERY PERFORMED ELSEWHERE

Case No.	*Surgery*
2	Lobectomy was performed and diagnosed as cancer in 1937. Presented herself to us with hard mass in the opposite lobe and positive lymph node metastases in 1943. Operation consisted of right lobectomy and block dissection of the right neck. Pathologic diagnosis was papillary adenocarcinoma
27	Had lobectomy at the age of 17, which was 22 years ago. This diagnosis was "benign." The recurrent nerve on that side was paralyzed. Now has a firm mass on the opposite side. She is now toxic—BMR plus 28—prepared with iodine and tapazole—reduced BMR to normal. A complete thyroidectomy was performed on April 29, 1952. No recurrence to date. Pathologic diagnosis: papillary adenocarcinoma
33	Had lobectomy 40 years ago. We were unable to obtain previous diagnosis but was said to be benign. Presented herself with a hard nodule in the right lobe. Complete thyroidectomy was performed on May 16, 1948, the pathologic diagnosis being papillary adenocarcinoma
32	Eight years ago, a left lobectomy was performed. Pathologic diagnosis was a nodule of papillary carcinoma. Now has a large hard mass in the right lobe with enlarged lymph nodes. A complete thyroidectomy with block dissection of the right neck was performed on May 11, 1948. The pathologic diagnosis was papillary adenocarcinoma in the thyroid gland and also in the lymph nodes. No recurrence to date
40	Two years ago, a total thyroidectomy was performed elsewhere, leaving only a small amount of thyroid on one of the sides. The diagnosis at the time of the previous surgery was papillary carcinoma. He presented himself to us with widespread metastases in the form of hard masses in the neck (see Fig. 8) and also in the mediastinum, lungs, spine, and bones. Death occurred soon

The matter of so-called "prophylactic gland dissection" needs clarification. In a great majority of cases, it has been impossible to determine clinically if there were positive lymph node metastases. Even during surgery it was impossible to identify lymph node metastasis with any degree of certainty. In the light of the knowledge that 50 to 70 per cent of the patients have positive glandular metastasis when first seen, it is obvious that gland resections should be performed at once. The thought of deliberately leaving live cancer cells in lymph nodes is intolerable. This is not adequate surgery, and sooner or later a crop of recurrences will appear which will make us regret any entertainment of the modern, conservative concept which has permeated our thinking. A good example is Case 40 described under "deaths."

The size of the thyroid tumor is no criterion upon which to base a decision relative to neck dissection. The patient described in Case 28, recently operated upon, had large masses of metastases in the neck, yet the primary cancer in the thyroid gland was only a few millimeters in diameter. Only complete thyroidectomy would remove such a primary lesion with certainty.

The extent of the block dissection of lymph nodes in the neck calls for discussion. First, there may be lymph nodes above and below the isthmus as well as between the strap muscles. Often overlooked are the esophageal nodes located behind the recurrent laryngeal nerve and the nodes in the superior mediastinum. Therefore, the usual surgical procedure is continued to remove the strap muscles and the chains of nodes which extend into the chest. The sternum is not

split, but with good light, this area can be cleared reasonably well from above. In the upper neck, the dissection should continue upward to include the suprahyoid areas, because many times positive nodes have been found right up to the base of the skull.

It is my conviction that many of my patients would be dead if radical neck resections had not been performed. It is known that a lymph node which contains cancer cells may disseminate these cells to other regions. Therefore, the nodes should be removed at the time the diagnosis of malignancy is made and its type established since these are not radiosensitive. A complete thyroidectomy is performed, plus a radical resection of the neck on the same side as the tumor. If positive glands are found, then the opposite side is also operated on, but here the jugular vein is often preserved and occasionally, the sternomastoid muscle. This can be retracted in various directions, and the neck can be cleared remarkably well. In a few instances, the muscle has been divided and sutured at the close of one operation. No operative mortality has occurred in the block dissection cases. There is a definite morbidity when the spinal accessory nerve is sacrificed. In young people, the resulting disability is slight, since they seem to be able to adjust more readily than patients in the older age group. The debility is never sufficient excuse for not performing the operation. The finding of "blood vessel invasion" in the microscopic examination does indicate malignancy and is helpful in making the diagnosis. The occurrence of blood space invasion does not necessarily mean that distant metastases are certain to occur. Certainly, such does not constitute an excuse not to perform adequate surgery in the neck. Four patients had "blood vessel invasion" and in not 1 of these cases has distant metastases occurred, although several years have elapsed.

In Table VII the cases of 4 patients operated upon elsewhere are reported. In each one, a lobectomy had been performed, and later, cancer appeared in the opposite lobe.

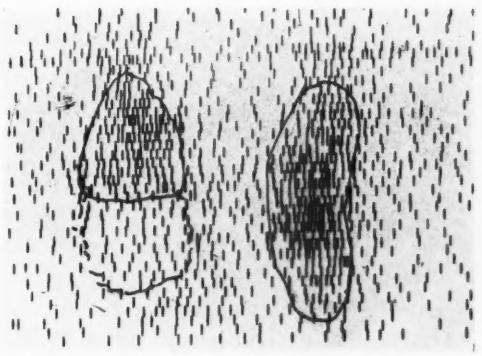


FIG. 1. Thyrogram showing an uptake of 19 per cent. There is a filling defect in the lower right lobe which proved to be an adenocarcinoma.

In at least 27 per cent of cases, cancer exists in both lobes. It certainly is inadequate surgery when only one lobe is removed for cancer.

The fifth case (Table VII) has been described under deaths (Table II). It may be repeated, for emphasis, that a thyroidectomy had been performed 2 years previously. No block resections were attempted and no follow-up with radioactive iodine. Now, he

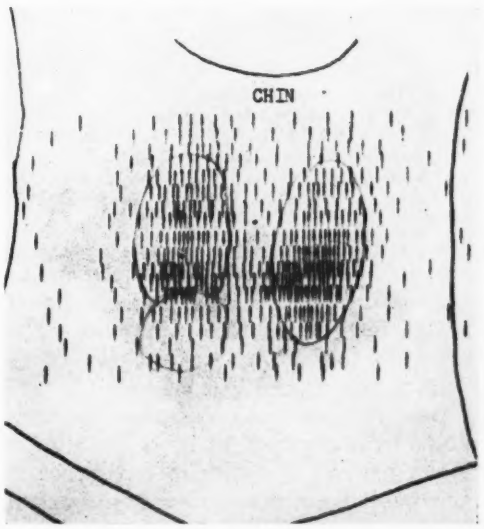
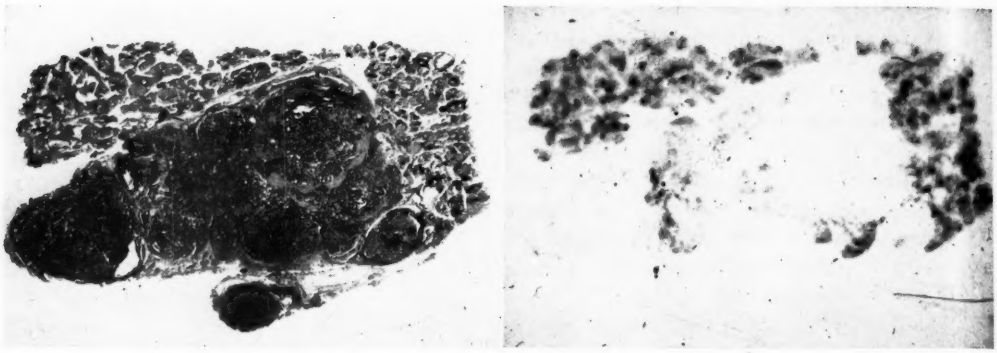
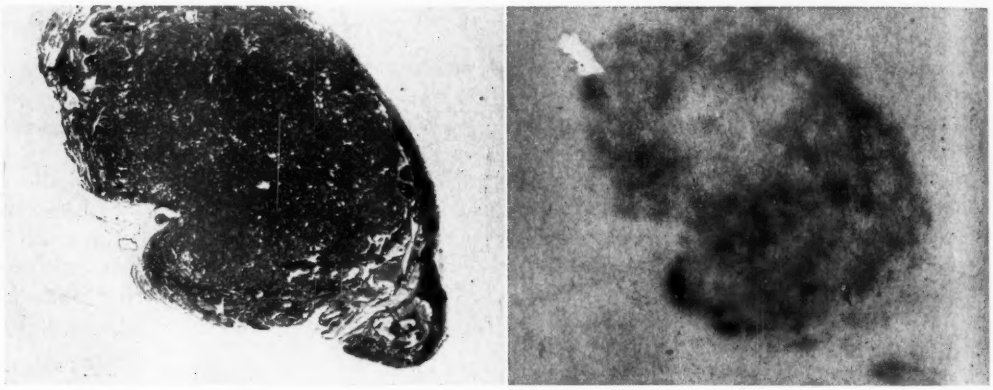


FIG. 2. A thyrogram taken before surgery. The uptake was estimated at 29.8 per cent. The lower right pole shows a filling defect. At this point a palpable mass could be felt which proved to be a malignant nodule.



a b

FIG. 3.



a b

FIG. 4.

FIG. 3. a, This section of thyroid reveals an adenocarcinomatous nodule with follicle formation. The fibrous capsule is penetrated by tumor cells. b, Radioautograph of the section shown in a. The normal thyroid tissue has absorbed the radioactive iodine. The tumor tissue, however, has taken the iodine up very poorly and in a very spotty manner.

FIG. 4. a, Section of a metastasis to a lymph node which is almost completely replaced by tumor cells. This is the same case as shown in Figure 3. b, Radioautograph of the lymph node seen in a. The iodine has absorbed better than in the original tumor (Fig. 3b). The uptake is still spotty and too deficient to be depended upon for therapeutic effect.

presented himself with widespread metastasis in the neck, mediastinum, lung, bones, and spine. I repeat that adequate lymph node resections are necessary following complete thyroidectomy. When multiple adenomas are found, complete thyroidectomy should be performed. To leave a portion of diseased gland is to invite recurrence of adenomatous goiter or a malignant tumor.

RADIOACTIVE IODINE (I^{131}) IN THYROID CANCER

In preoperative studies of goiter cases the basal metabolism is still useful and probably the most widely used. There is quite a percentage of error in these tests, and many discount the value of the results. Protein bound blood iodine tests are better but often are erroneous because of the previous consumption of iodine in salt or otherwise. A previous gallbladder x-ray study with an iodine preparation will throw the result off. Radioactive iodine uptake studies are much more reliable. The normal range of uptake of iodine is from 10 to 35 milligrams per cent. Thyrograms (Figs. 1 and 2, 5 to 8) are useful in demonstrating the distribution of

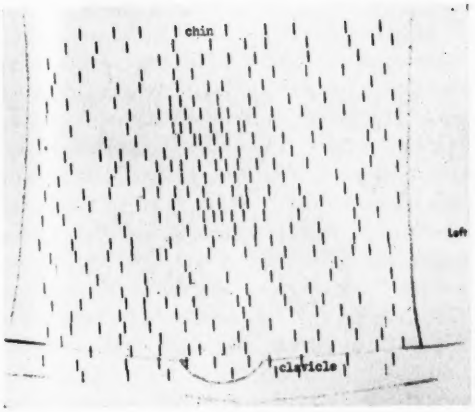


FIG. 5.

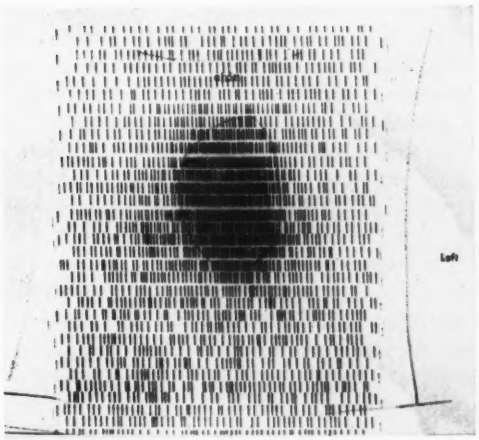


FIG. 6.

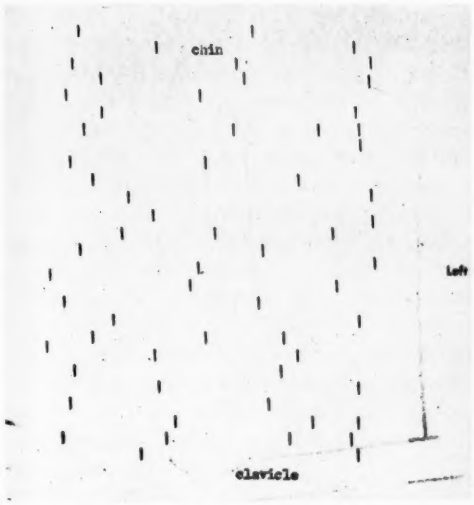


FIG. 7.

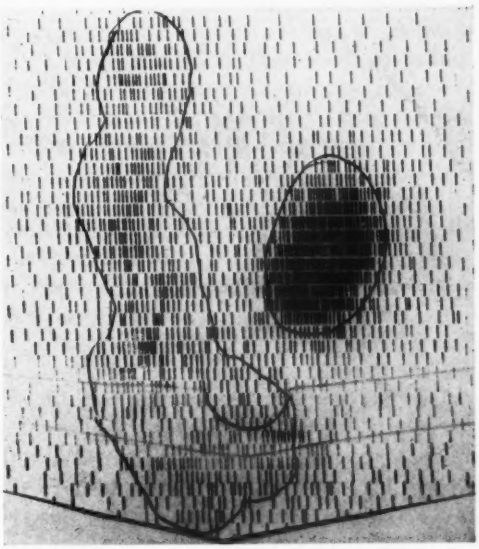


FIG. 8.

FIG. 5. Postoperative thyrogram gave an uptake of 6.5 per cent and, therefore, showed some suspicion of residual thyroid tissue in the midline high up. A second dose of I^{131} was then given after administration of thyroid stimulating hormone.

FIG. 6. This thyrogram is of the same case as shown in Figure 5, after injection of thyroid stimulating hormone. It shows a marked increase of uptake in the upper central portion of the neck and also demonstrates how we hope to stimulate metastases to increased absorption of I^{131} by accelerating the activity.

FIG. 7. A later thyrogram of the same patient as in Figures 5 and 6. Treatment has been given with I^{131} and the residual thyroid (after surgery) has entirely disappeared. If metastases now develop, they are given the best possible chance to take up radioactive iodine.

FIG. 8. Thyrogram of Case 40, taken when first seen by me. This patient had been operated on previously elsewhere. Almost a complete thyroidectomy had been performed, but there was no further surgery or follow-up. The tumor mass recurred in the right lobe and extended into the mediastinum, and a hyperplastic lobe appeared on the left side. The uptake was 29.8 per cent, which is in the high normal range. This patient had widespread metastases in the lungs, mediastinum, bones, and spinal cord, as well as the recurrence in the neck. One cannot resist the thought that if adequate surgery and proper follow-up treatment had been carried out, perhaps this patient's untimely death could have been averted.

the iodine within the gland. A filling defect (Figs. 1 and 2) may indicate a malignant nodule. It may be due to other conditions, however, such as an area of fibrosis, cystic degeneration, or a nonfunctioning adenoma. "Screening" the whole body is now a common procedure to see if there is any increased uptake which might indicate metastases.

In those cases in which cancer is really suspected an "uptake dose" of radioactive iodine is given 24 hours before surgery in order to obtain material for a radioautograph (Figs. 3b and 4b). The removed thyroid tissue is imbedded in paraffin for sectioning and some unstained slides are used for the radioautograph. These are exposed to photographic film, and when this is developed, it gives us the radioautograph similar to those seen in Figures 3b and 4b. When Figure 3b is compared with Figure 3a, it is seen that the tumor tissue takes up the iodine poorly and in a spotty manner. The metastasis to a lymph node is shown in Figures 4a and 4b. Here again, the uptake is poor and uneven. This case was of a papillary adenocarcinoma. This type of picture leads to a pessimistic outlook which I am sure is unwarranted. It is true that the uptake of iodine is never good enough to justify its sole use in these cancer cases. The uptake of iodine is poorest in the papillary type of carcinoma. Alveolar types absorb iodine much better. Therefore, the thyroid gland should be removed completely, following which a thyrogram should be taken, and if any areas in the neck show an uptake of radioactive iodine these should be ablated by a dose of the radioactive iodine. Figure 5 shows a suspicious area of uptake. A stimulating dose of thyrotropic hormone was given and another thyrogram (Figure 6) was taken showing the marked increase in uptake of iodine. Radioactive iodine was then given in treatment amounts, and this successfully ablated the thyroid tissue, with the result shown in the thyrogram (Fig. 7). The practical application of this principle is that after ablation of all thyroid tissue in the neck, metastasis is very unlikely to occur by the lymphatic routes. However, if any metastasis does appear, it will be bombarded by the thyrotropic hormone which originates in the pituitary gland with activation of the metastases, which, in turn, causes the absorption of iodine. This action is accelerated by injections of thyrotropic hormone and the thiouracil drugs are also useful. That these drugs do affect the uptake of radioactive iodine was demonstrated in thyrograms (Figs. 5, 6, and 7). In cases in which the primary tumor was papillary and the radioautograph demonstrated poor absorption, many are showing much better uptake in the metastases. One patient had metastasis in both lungs which cleared completely with radioactive iodine treatment. The patient is well and free from metastases 6 years later. Every case of cancer of the thyroid gland should be followed by radioactive iodine studies and any uptake ablated with radioactive iodine treatment.

Figure 8 is the thyrogram of a patient operated upon (elsewhere) 1½ years previously. An "almost total" thyroidectomy was performed. No block resection or follow-up was given. The thyrogram demonstrates huge recurrences in the neck which show a marked degree of radioactive iodine uptake. Treatment by adequate surgery with follow-up with radioactive iodine might have given this patient a better chance of survival.

In my opinion, therefore, all thyroid tissue in the neck should be removed surgically and any residual ablated by radioactive iodine treatment. In other words, the minimum operation is complete thyroidectomy plus block dissection of the neck on the side of the cancer. If nodes on this side are negative, then there is no need to operate again on the opposite side. If the lymph nodes are positive, then block resection is performed on the opposite side. In this case, however, the jugular vein is usually left.

Sometimes during operation in these cases it is difficult to be immediately sure that cancer is present. Most pathologists will not be certain enough to make a diagnosis of a

frozen section. Some, however, will feel confident enough to do so. The finding of a metastatic lymph node clinches the matter. If the diagnosis of cancer is certain, then complete thyroidectomy with block dissection of the one side of the neck is performed all in one stage. If there is doubt, the report on the paraffin sections is awaited and operation is performed a second time.

Following the completed surgical treatment, all cases are followed by radioactive iodine studies as outlined.

SUMMARY

1. Cancer of the thyroid gland, no matter what the pathologic classification, must be considered a potentially fatal disease. As such, it should be treated vigorously with all the means at our command.

2. Nothing short of total thyroidectomy together with block dissection on the same side constitutes adequate surgery.

3. Radioactive iodine is used to ablate any remaining thyroid tissue in the neck. Should metastases occur subsequently, they then would be more likely to take up radioactive iodine.

REFERENCES

1. COHEN, MORLEY, and MOORE, GEORGE E. Malignant lesions of the thyroid. Surgery, 1954, 33: 62.
2. EGNARK, A., LARSSON, L. G., LILJESTRAND, A., and RAGNHULT, INGER. Iodine concentrating thyroid carcinomas; a report of 3 cases. Acta radiol., Stockh., 1953, 39: 423.
3. MCCLINTOCK, JOHN C., STRANAHAN, ALLAN, ALLEY, RALPH D., and BAKER, WILLIAM A. Thoraco-cervical approach for malignant disease of the thyroid gland. Ann. Surg., 1954, 139: 158–165.
4. SOKAL, J. E. Occurrence of thyroid cancer. N. England J. M., 1953, 249: 393.

SURGICAL TREATMENT OF OCCLUSIVE CORONARY ARTERY DISEASE BY ENDARTERECTOMY OR ANASTOMOTIC REPLACEMENT

KAREL B. ABSOLON, M.D., JOSEPH B. AUST, M.D.,
RICHARD L. VARCO, M.D., F.A.C.S., and C. WALTON LILLEHEI, M.D., F.A.C.S.,
Minneapolis, Minnesota

CLEARLY THE BASIC PROBLEM in occlusive coronary artery disease is the diminished blood supply to the functioning myocardium. For many years attempts have been made to increase this blood supply by indirect methods involving the creation of anastomotic channels using grafts of muscle, lung, intestine, or spleen; scarification of myocardium and introduction of fibrosing materials into the pericardial space, ligation or arterialization of the coronary sinus, implantation of systemic arteries into the myocardium, to mention but a partial list of suggested approaches.

The benefits of these indirect procedures in the therapy of coronary artery disease in man have been equivocal. Obviously, if the obstructed or occluded arteries could be reopened by successful removal of the actual obstructing plaques, there would be no doubt about the therapeutic benefits derived by the patient. This more direct approach to the problem has appealed to us on the basis of the known incidence of localized coronary artery obstructions. For example, Schlesinger has found that 69 per cent of the occlusions in the main stems of the coronary arteries were localized in the proximal 4 centimeters of these vessels (Fig. 1). Schlesinger and others also have emphasized that in these same patients with serious main artery coronary disease their distal ramifications may be but little involved or entirely normal in appearance. Moreover, another consideration in regard to direct procedures is the historical observation that surgery frequently has achieved its most dramatic successes in dealing with mechanical obstructions existing in the urinary tract, biliary tract, intestinal tract, or blood vessels elsewhere in the body.

These considerations have been the initiating stimulus for these experimental investigations upon direct surgery of the coronary artery.

From the Department of Surgery, University of Minnesota Medical School, Minneapolis.

Supported by research grants from the: Graduate School, University of Minnesota, Minnesota Heart Association, Life Insurance Medical Research Foundation, National Heart Institute, U.S.P.H.S. (H-830), and the Fund for Surgical Therapy of Coronary Artery Disease.

METHOD OF STUDY

In these investigations two approaches to direct improvement of coronary artery blood flow have been studied. These were (1) endarterectomy and (2) resection of a segment of coronary artery with anastomotic replacement. The endarterectomies of the coronary artery were carried out in the autopsy room upon fresh cardiac specimens from elderly patients with varying degrees of arteriosclerosis. These procedures were done both to ascertain their feasibility and to develop suitable surgical techniques as well. Also, in these human specimens, segments of peripheral arteries were used for end-to-end and end-to-side anastomoses to the coronary arteries.

On the basis of these observations it appeared feasible to study various types of anastomotic procedures in vivo in mongrel dogs. Three types of anastomotic replacement

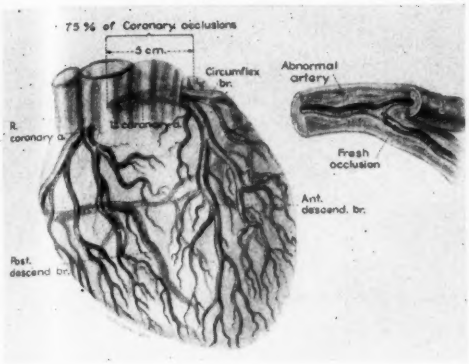


FIG. 1.

FIG. 1. Percentage of localization of coronary occlusions. Three-quarters of the serious or fatal obstructions occur in the first 2 inches of the coronary arteries. This fact is an important circumstance predicting success in the removal of these obstructions by direct surgical methods in selected patients.

FIG. 2. Coronary artery endarterectomy technique. After 2 incisions, 5 millimeters in length, have been made at opposite ends of the coronary artery, the diseased occluding sequestrum is being dissected free by means of spoon-shaped and loop-shaped endarterectomy instruments.

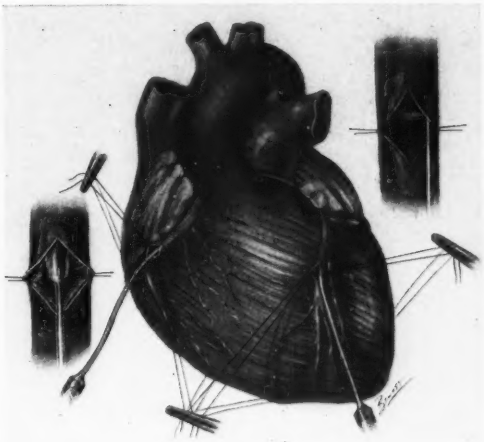


FIG. 2.

were studied in these animals. These were: carotid artery to left circumflex coronary artery, internal mammary to left circumflex coronary artery, and left subclavian artery to left circumflex coronary anastomosis utilizing a synthetic (ivalon) prosthesis to bridge the gap. These various anastomoses were made end-to-end for the most part by utilizing fine silk (No. 6–0).

RESULTS

Endarterectomy. These observations were based upon studies made on the hearts of 10 cadavers. Endarterectomy of small segments was done in 2 cadaver hearts by the commonly used technique for ileofemoral endarterectomy. The coronary arteries were incised longitudinally over their occluded or stenotic segments and after removal of the

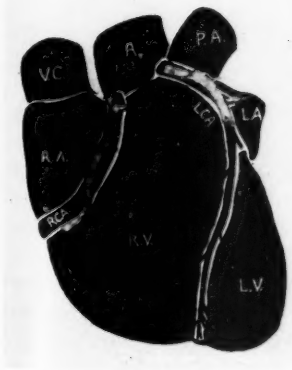


FIG. 3.

FIG. 3. Coronary artery endarterectomy specimens. These are typical obstructing sequestra consisting of the intima and a portion of the media removed in the autopsy room from a patient with coronary arteriosclerosis.

FIG. 4.

FIG. 5.

FIG. 4. In vitro coronary angiogram of autopsy specimen from 76 year old man; arrow indicates obstruction.

FIG. 5. Coronary angiogram. Same specimen as seen in Figure 4 after coronary artery endarterectomy.

FIG. 6. Anastomoses between subclavian artery (*LSA*) and circumflex branch of left coronary artery (*LCA*), utilizing a molded synthetic vessel (ivalon) to bridge the gap. (Dog—in vivo).

occluding atheroma the arterial wall was reconstructed by use of a continuous No. 6-0 silk stitch. Technically this procedure was possible not only in the main coronary arteries of these fresh specimens, but also beyond the first bifurcation of either the right or left main coronary artery. In the other 8 specimens an alternative technique was found to be of value particularly for longer segments of occlusion. This procedure involved the use of a "tunneling technique" which was carried out by making 2 incisions 5 millimeters long at opposite ends of the involved artery; through these incisions the dissection of the diseased sequestrum from the remaining viable artery wall was carried out with spoon-shaped and loop-shaped endarterectomy instruments (Fig. 2). This intimal tube then was transected at the proximal end and pulled through the proximal incision. By this technique not only the main artery intima could be removed, but also the intima of its branches could be carried along (Fig. 3). The reconstruction of the artery could be carried out rather rapidly as there were only 2 short incisions to be sutured. Significant difficulties were encountered in dissecting the coronary arteries in 2 of 8 cadaver hearts. In these 2 specimens calcified plaques penetrated through the entire thickness of the wall and full thickness tears occurred. Another noteworthy observation in carrying out this endarterectomy procedure was the fact that in most of the coronary arteries only a paper thin wall remained, although it resisted pressures elicited by forcibly injecting a radio-opaque substance via a syringe. The segments of peripheral arteries of corresponding size were anastomosed in 2 hearts either end-to-end or end-to-side to the coronary arteries beyond the bifurcation. Although few in number, these anastomoses were readily accomplished by utilizing fine silk under these ideal circumstances.

SYSTEMIC TO CORONARY ARTERY ANASTOMOSES

Ivalon prosthesis (Fig. 6). In this group, 15 dogs were operated upon with a postoperative mortality of 5 animals within the first 24 hours. Eight dogs survived from 24 hours up to 3 weeks. The shunts in each of these 8 animals were occluded with thrombi on postmortem examination. Two dogs in this series are alive at present and can be classified as long term survivals.

Cone-shaped tubes of the plastic ivalon were constructed by boiling 20 minutes while held compressed in a mold, with a lumen approximately equal to the diameter of the dogs' subclavian artery at one end and the other small enough for insertion into the circumflex branch of the left coronary artery. The subclavian artery was anastomosed to the ivalon tube, then the circumflex branch of the left coronary artery was ligated, incised, and the prosthesis inserted into the coronary artery. Only 1 stitch was necessary to hold this prosthesis within the artery. Since ivalon softens when it comes in contact with blood, it was necessary to keep it dry to maintain the stiffness for insertion into the coronary artery.

Systemic artery anastomoses. Twenty-seven dogs were operated upon in this group.

FIG. 7.

FIG. 8.

FIG. 9.

FIG. 10.

FIG. 7. Internal mammary (*IMA*) to left circumflex coronary artery (*LCA*), end-to-end anastomosis. Temporary by-pass with polyethylene tube (*PE*) permitting anastomosis. (Dog—in vivo, *LSA:* left subclavian artery).

FIG. 8. Internal mammary (*IMA*) to left circumflex coronary artery anastomosis completed. By-pass shunt removed. *LSA:* left subclavian artery.

FIG. 9. Left carotid artery (*LCA*) to circumflex artery anastomosis (arrow), polyethylene tubing by-pass (*PE*) supplies the heart with oxygenated blood until the anastomosis is completed.

FIG. 10. Left carotid artery (*LCA*) to left circumflex coronary artery anastomosis accomplished. *LSA*: left subclavian artery.

Eight survived this operation but 6 died later in the postoperative interval. Two dogs were long term survivors. In all of the animals of this group dying within the first week, the anastomoses were open at autopsy. In those dogs which died or were sacri-

ficed later, one-half of the anastomoses were open.

The internal mammary artery was anastomosed to the circumflex branch of the left coronary artery in 12 dogs. The main physiologic consideration was to maintain an adequate blood supply to the myocardium since ligation of the left coronary artery to allow an anastomosis invariably will lead to fatal ventricular fibrillation in a few minutes. The anastomoses of the end-to-end type were performed over a polyethylene tube shunt inserted through the cut end of the subclavian artery just distal to the take-off of the internal mammary artery, so that one end lay in the aorta and with the remainder of the shunt tubing looping out of the transected subclavian. Then, the other end of the shunt was reinserted into the cut end of the subclavian artery through the internal mammary artery and into the left circumflex coronary carrying blood to the coronary arterial bed distal to the anastomotic site (Fig. 7). After finishing the anastomosis, the polyethylene tube was removed, and the subclavian artery distal to the take-off of the internal mammary artery was ligated (Fig. 8).

The left carotid artery was dissected in the neck and brought into the chest cavity for anastomosis to the circumflex branch of the left coronary artery in 15 animals. End-to-end and end-to-side anastomoses were carried out over polyethylene tubes carrying blood from the animals' own aorta through the left subclavian artery (Figs. 9 and 10). The acute surgical mortality was caused by ventricular fibrillation in every case when the polyethylene shunt supplying the heart muscle either was not inserted within 4 minutes or if the blood clotted in the shunt during the time utilized for the anastomoses.

DISCUSSION

The purpose of this study was to ascertain the technical feasibility of direct surgical procedures on the coronary arteries in man. Mortality was not the major consideration in the present animal studies but the fact that even some dogs were long term survivors has demonstrated the technical feasibility of anastomotic procedures even in these small vessels. The high incidence of ventricular fibrillation noted during the anastomotic procedures emphasizes the need for total cardiac by-pass with a pump oxygenator in order to reduce the hazards of this complication. Such experiments are now in progress utilizing the simple pump-oxygenator system developed in this clinic (1). However, in human hearts, when complete occlusion already exists, it may be argued that no further deprivation of blood supply to the myocardium would occur by the techniques described.

During experimental and clinical cardiac surgical procedures, we have been favorably impressed by the relatively much larger size of the coronary arteries in the living state as compared with their size in the collapsed state even immediately after death. Formalin fixation further shrinks these vessels. It seems likely to us that the small size of the coronary arteries has constituted more of a psychologic than an actual mechanical barrier to consideration of direct procedures upon these vessels designed to augment blood flow to the myocardium.

We have studied several possible approaches for direct coronary arterial replacement of the first segment. The direct suture technique of anastomosis was superior to the use of an ivalon prosthesis. The continuously contracting heart presents some difficulties in performing the delicate anastomotic procedures necessary and in addition to support of the organism by a pump-oxygenator system temporarily induced cardiac standstill with or without retrograde perfusion of the coronary sinus with arterialized blood may be desirable.

SUMMARY

The feasibility of endarterectomy in coronary arteries of human cadavers was established. Direct systemic to coronary artery

anastomoses were performed in dogs in vivo with survivors and in cadaver hearts. The merit of such procedures has been discussed, and some of the technical difficulties and physiopathologic problems involved are defined.

REFERENCES

1. Lillehei, C. W., DeWall, R. A., Read, R. C., Warden, H. E., and Varco, R. L. Direct vision intracardiac surgery in man using a simple, disposable artificial oxygenator. Dis. Chest, 1956, 29: 1–8.
2. Schlesinger, M. J., and Zoll, P. M. Incidence and localization of coronary artery occlusions. Arch. Path., 1941, 32: 178.

MALIGNANT LESIONS OF THE NIPPLE EXCLUSIVE OF PAGET'S DISEASE

GORDON H. CONGDON, M.D., and MALCOLM B. DOCKERTY, M.D.,

Rochester, Minnesota

PRIMARY MALIGNANT NEOPLASMS arising from the epithelium and underlying connective tissue of the nipple are extremely rare. The literature on the subject is comprised mostly of reports of isolated cases and periodic analyses on accumulated data from these reports. Considerable confusion exists regarding the clear-cut histopathologic separation between carcinomas and papillomas, the latter of which often expand the nipple and give rise to a serous and bloody discharge similar to that observed in papillary and comedocarcinoma. The weeping eczema of Paget's disease was at one time attributed to primary carcinoma of the nipple. Inasmuch as various authors consider the skin lesions of Paget's disease to represent intraepithelial metastasis from an underlying mammary carcinoma, such cases have been deleted from the present study. Deleted also were several cases in which cellular papillomas had been erroneously "overdiagnosed." Tumors exceeding 2.5 centimeters in diameter also were excluded because it was impossible to be certain of the site of their origin.

From the Section of Surgical Pathology, Mayo Clinic and the Mayo Foundation, Rochester, Minnesota.

Abridgment of thesis submitted by Dr. Congdon to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

In 1912 Schreiner reported a case of cylindrical cell carcinoma arising in the epithelium lining the ducts of the nipple. He reviewed the literature to that date and found reports of 37 cases of primary benign and malignant tumor of the nipple. These he included in his own study.

In 1913, Battle and Maybury reported a case of primary epithelioma of the nipple in a girl aged 11 years. About 18 years later, in 1931, Cheatle and Cutler classified carcinoma of the nipple, and in the same year Fisher described a condition that he called "phantom tumor of the breast" in which discharge from the nipple occurred with no palpable tumor present.

In March 1955, Jones reported 5 cases of so-called "benign florid papillomatosis" of the nipple. The condition is usually accompanied by discharge from the nipple, erosion, erythema, and enlargement. A diagnosis of Paget's disease is usually made clinically. A picture of benign papillary and adenomatous epithelial overgrowth is seen microscopically in the nipple.

EMBRYOLOGY AND ANATOMY

Embryology. As in all mammals, the human breast develops in a primitive epidermal thickening known as the milk line, which

TABLE I.—MALIGNANT LESIONS OF THE NIPPLE

Type of carcinoma, (cases)	*Grade of tumor*	*Axillary nodes, evidence of carcinoma*	*Treatment*		*Survival after operation*
			Surgical	*X-ray**	
Adenocarcinoma (25)					
Scirrhous (15)					
1	1	Neg.	Simple	No	Living and well, 16 yrs.
2	2	Neg.	Simple	Yes	Died 11 mos. later; obstruction of bowel
3	2	Neg.	Semiradical	No	Died 7 yrs. later; stroke
4	2	Neg.	Radical	No	Living and well, 1 yr.
5	3	Pos.	Radical	Yes	Living and well, 7 yrs.
6	3	Neg.	Radical	No	Living and well, 13 yrs.
7	3	Neg.	Radical	Yes	Died 7 yrs. later; stroke
8	3	Neg.	Radical	No	Died 1 yr. later; cause unknown
9	3	Pos.	Radical	Yes	Metastasis to lumbar region 1 yr. later
10	3	Pos.	Radical	Yes	Living and well, 18 mos.
11	4	Pos.	Semiradical	Yes	Living and well, 8 yrs.
12	4	Pos.	Radical	Yes	Died with recurrence 7 yrs. later
13	4	Neg.	Radical	No	Living and well, 18 mos.
14	4	Neg.	Radical	Yes	No follow-up
15	4	Pos.	Radical	No	Died 6 mos. later; carcinomatosis
Comedo (7)					
16	1	Neg.	Radical	No	Living and well, 13 yrs.
17	2	Neg.	Simple	No	Living and well, 3 yrs.
18	2	Pos.	Simple	Yes	Living and well, 5 yrs.
19	2	Neg.	Radical	Yes	Living and well, 25 yrs.
20	3	Neg.	Radical	Yes	Living and well, 16 yrs.
21	3	Neg.	Radical	Yes	Living and well, 11 yrs.
22	3	Pos.	Radical	No	Living and well, 4 yrs.
Papillary (2)					
23†	2	Neg.	Simple	Yes	Eleven years after the first operation a similar lesion developed in the opposite (left) breast and was treated by simple mastectomy. This lesion did not receive x-ray treatment
24	3	Pos.	Radical	Yes	Living and well, 2 yrs.
Mucous (1)					
25	3	Neg.	Radical	Yes	Died 2 yrs. later; metastasis
Squamous cell (2)					
26	1	No nodes	Simple	No	Known to have survived 11 yrs. without recurrence
27	4	No nodes	Radical	No	Died 3 yrs. later, cerebrovascular accident; no recurrence
Basal cell (2)					
28	1	No nodes	Simple	No	No recurrence at time of follow-up, 1 yr. later
29	1	No nodes	Simple	No	No recurrence at time of follow-up, 2 yrs. later

*After operation.
†A recurrence developed in the right breast several years after the initial treatment. This was excised, no x-ray treatment was given, and patient has not had a further recurrence.

extends bilaterally on the ventral surface between the attachments of the upper and lower limbs. In the human embryo, the milk line appears at about the sixth week. This primitive line then gradually atrophies, but at the ninth week the site of the permanent mammae can be recognized by localized persistence of the epithelial thickening. The primitive nipple buds are formed at this time. By the sixth month of development, some 15 to 20 solid epithelial cords extend into the corium from the basal layer of the primitive nipple. By the ninth month these branching cords have developed lumens and may have 2 or 3 layers of cells.

Anatomy. The adult female breast is a modified compound alveolar secretory gland derived from the skin. It is composed of approximately 20 irregular lobes radiating from the central part of the nipple. Each

lobe has an excretory duct, exhibiting beneath the nipple a local dilatation known as the "sinus lactiferous." The ducts do not anastomose, although 2 or more may possess a common opening at the nipple. They branch numerous times forming lobes, and end in clusters of epithelial cells (lobules), which constitute the parenchyma. The elastica of the ducts terminates as the latter divide to form lobulations. The terminal buds are called "alveoli" and are present only in the adult female breast (absent in the male).

Large ducts at the nipple are lined by stratified squamous epithelium which gradually merges with the columnar cells of the smaller subdivisions. The peripheral portions contain low columnar cells which are frequently disposed in two layers and which blend into the cuboidal cells of the lobules.

MATERIALS AND METHODS

In approximately 10,000 cases of malignant disease of the breast in which operations have been done at the Mayo Clinic since 1910, the disease could be proved to have originated in the nipple in only 29. These 29 cases comprise the basis for the present study.

Histories were abstracted for pertinent clinical data. All gross specimens had been preserved in 10 per cent formalin solution, and these were assembled for scrutiny. The size and position of each growth were carefully noted and the data recorded. Observations were made similarly regarding ulceration of the overlying skin of the nipple. Fresh blocks of tissue were then cut from representative regions, including axillary nodes when the latter were available. These specimens were placed in bottles of fresh formalin, embedded in paraffin, sectioned, and stained routinely with hematoxylin and eosin. Original slides made at the time of operation were added to the new collection. A clinical and pathologic correlation was finally attempted on the basis of data obtained.

FIG. 1. Case 12. Adenocarcinoma of nipple, grade 4. Patient had axillary nodal involvement and died 7 years after operation. Metastasis to the lungs and skin had developed. She was 49 years of age and had had retracted nipples and slight eczema for only 3 months. Hematoxylin and eosin, ×73.

CLINICAL FINDINGS

The study of the cases of 29 patients who exhibited malignant lesions of the nipple revealed that 82 per cent of the patients were women and 18 per cent were men. The average age for the entire group of patients was about 58 years, the youngest being 39 years of age and the oldest 83. The average age for women having adenocarcinoma was 54.9 years. Ninety-one per cent of the women were married, and 66 per cent had had 1 or more normal pregnancies and de-

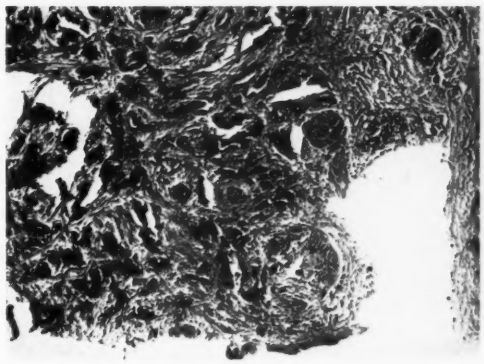


FIG. 2. Case 13. Adenocarcinoma of the nipple, grade 4, scirrhous type, with perineural involvement. The patient, a 67 year old white woman, had sharp shooting pains and redness in the nipple of 5 months' duration. Hematoxylin and eosin, ×73.

FIG. 3. Case 3. Preclinical Paget's disease with underlying scirrhous and comedo adenocarcinoma, grade 2, with areas of calcification. This lesion occurred in the nipple of a 74 year old woman who gave a history of intermittent pain of 1 year's duration, no discharge and retraction of the nipple for 1 year. Hematoxylin and eosin, ×73.

liveries. A family history of cancer in some organ was reported by 51 per cent of the patients, and the mothers of 2 patients had died from carcinoma of the breast. Sixty-three per cent of the lesions involved the left side and 37 per cent, the right. The average duration of symptoms for the women was 11 months and for the men, 7.6 months. A third of the women had pain; none of the men had pain. Half of the women and a third of the men had retracted nipples. Fourteen per cent of the entire group exhibited ulceration of the nipple; 20 per cent, eczema of the nipple; 20 per cent, induration of the nipple; and 34 per cent, enlargement of the nipple. Some type of discharge from the nipple was present in about 48 per cent: in 13 per cent it was serous, in 17 per cent bloody, and the term "serosanguineous" was employed to describe the discharge in 17 per cent. Seventy-five per cent of the patients had a tumor or enlargement of the nipple: 41 per cent noted a palpable tumor and an additional 34 per cent complained of enlargement. Axillary nodes were palpably enlarged in 38 per cent but, of these, only 17 per cent were positive for carcinoma. Five patients (17 per cent) whose axillary nodes were not recorded as being enlarged at the time of the clinical examination were found to have positive evidence of carcinoma on microscopic examination. Clinical appraisal of the condition of axillary nodes in primary carcinoma of the nipple obviously was difficult.

TABLE II.—GRADE AND TYPE OF PRIMARY MALIGNANT LESIONS IN THE NIPPLE (29 PATIENTS)

	Grade of lesion				Total No. of
Type of lesion	*1*	*2*	*3*	*4*	*lesions*
Adenocarcinoma	2	8	11	5	26*
Squamous cell carcinoma	1 (man)	.	..	1 (woman)	2
Basal cell carcinoma	Not graded				2†
Total					30

*One male had bilateral carcinoma of the nipple, the lesions occurring 11 years apart.
†One basal cell carcinoma appeared in a man, 1 in a woman.

TABLE III.—INCIDENCE OF METASTASIS TO AXILLARY NODES

Type of adenocarcinoma	*No. of cases*	*No. with positive axillary nodes*
Scirrhous	15	6
Comedo	7	2
Papillary	2	1
Mucous	1	0
Total	25	9

PATHOLOGIC FINDINGS

Gross appearances. The size of the lesions varied from 2.5 centimeters to a few millimeters. Gross features with reference to ulceration of the skin, the presence of discharge, and so forth have been described previously and these need not be repeated. Gross differences in the various types of lesions could be noted even after fixation with formalin.

The scirrhous carcinomas were very hard and the extent of their invasion frequently was poorly demarcated. Fifteen of the lesions (2 involving male breasts) were of this type.

In 6 cases, plugs of tumor characteristic of comedocarcinoma could be expressed from the nipple.

In our single case of mucous cancer, distinguishing gross characteristics were not exhibited; neither were they exhibited in the 3 papillary growths.

Lesions on the surface of the nipple could not be differentiated grossly into basal, squamous, or adenocarcinomatous types.

Microscopic aspects. Microscopically, the various types of malignant diseases of the nipple could be subdivided into adenocarcinoma, squamous cell carcinoma, and basal cell carcinoma (Table I). In 34 per cent of the cases of adenocarcinoma, positive axillary nodes were present. Positive axillary nodes were not present in any of the cases of squamous or basal cell carcinoma.

Adenocarcinoma included those lesions in which a tendency toward glandular differentiation existed. Four general types (25 cases) were noted: scirrhous, which included 1 tumor diagnosed as preclinical Paget's disease, comedo, papillary, and mucous adenocarcinomas. Comments on each of these types follow:

Scirrhous type (15 cases).—Fibrous tissue was prominent in these tumors, which featured cords and plugs of glandular epithelium with varying success in attempts to form glandular acini. Low grade (Broders' classification) lesions showed good gland formation, whereas there was less and less tendency toward formation of glands with the higher grade lesions, which spread through the nipple in sheets and cords (Fig. 1). The majority of lesions were graded 3 and 4. They tended to invade perineural lymphatics (Fig. 2). Ulceration, with replacement of surface epithelium by glandular epithelium, was present in 1 case. The grade of lesions and incidence of metastasis of this and other types of carcinoma are given in Tables II and III.

Preclinical Paget's disease was the diagnosis in 1 case. Large, clear, malignant (Paget's) cells that occurred singly and in clumps within the epidermis were the necessary condition for the diagnosis of Paget's disease. This disease is ordinarily looked upon as a clinical condition characterized by an eczematoid reaction on and about the nipple. It is always associated with an underlying carcinoma, usually of comedo type, and as indicated, the overlying skin exhibits the presence of Paget's cells. In our single case in which Paget's disease was proved microscopically, the skin changes were so early as to be unrecognizable clinically, and the "underlying" comedo and scirrhous growth appeared to be confined entirely within the anatomic bounds of the nipple (Fig. 3). For these reasons, we have included this case as 1 of our series of carcinomatous lesions primary in the nipple, and it is included in our statistics and in the tables as a case of scirrhous carcinoma.

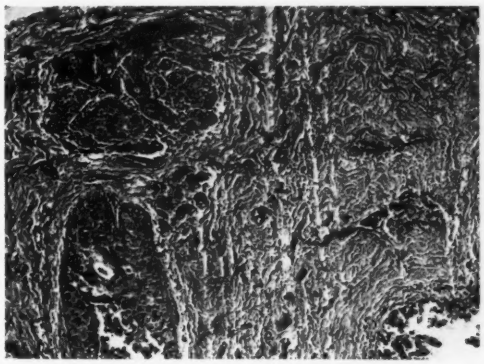


FIG. 4. Case 20. Comedo adenocarcinoma of the nipple, grade 3, associated with lobular carcinoma in situ. A 52 year old white woman had first noticed a swelling in her nipple 5 weeks before coming to the clinic. The presence of the lobular carcinoma suggested that the carcinoma was multicentric in origin. This section is cut so as to include some of the underlying tissue of the breast. Hematoxylin and eosin, ×73.

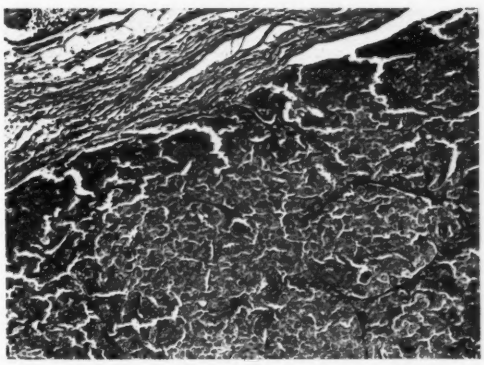


FIG. 5. Case 17. Papillary and comedo adenocarcinoma of the nipple, grade 2, with infiltration. Multicentric and of unknown duration occurring in an 83 year old white woman. Simple mastectomy was performed. The patient was living and well at the time of follow-up 3 years subsequently. Hematoxylin and eosin, ×73.

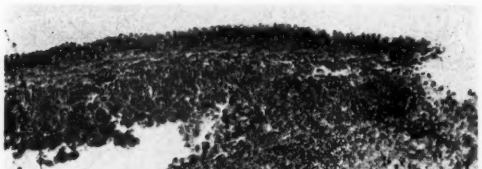


FIG. 6. Case 27. Squamous cell carcinoma of the nipple, grade 4, in an 80 year old white woman who had noticed tenderness and a bloody discharge from the enlarged nipple for 1 week. Hematoxylin and eosin, ×73.

Comedo adenocarcinoma (7 cases).—These neoplasms characteristically appeared basically as multicentric growths arising in, and being apparently confined for some time to, the major mammary ducts. An apparent difference between this growth as seen in the nipple and as seen in the breast proper is the frequent presence of necrotic cores of tissue in the central portion of the malignant plugs (Fig. 4).

Papillary adenocarcinoma (2 cases).—This type of neoplasm is characteristically a low grade tumor and clinically is rarely seen to metastasize, though in our series 1 patient had positive axillary nodal involvement. Soft papillary gland-containing excrescences were characteristic, as seen in Figure 5. Several layers of epithelial cells formed a mantle over cores of connective tissue. The epithelial cells contained dark staining, and sometimes bizarre, nuclei with occasional mitotic figures. The absence of a limiting membrane helps to differentiate this lesion from benign papilloma.

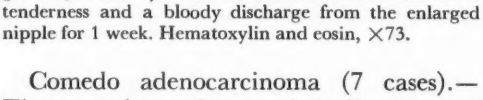


FIG. 7. Case 26. Squamous cell carcinoma of the nipple, grade 1, in a 52 year old white man who had noticed eczema and a bloody discharge from the enlarged nipple for 2½ months. Hematoxylin and eosin, ×37.

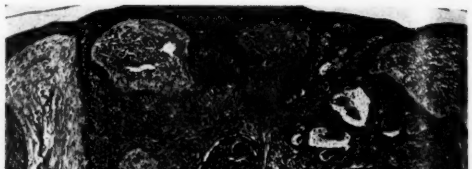


FIG. 8. Case 29. Pigmented basal cell carcinoma of the nipple in a 43 year old white man whose mother had died of carcinoma of the breast. Hematoxylin and eosin, ×37.

Mucous adenocarcinoma (1 case).—This high grade lesion with little connective tissue and large amounts of mucus within the cells and interspaces showed perineural involvement and ulceration of the nipple. Good illustrations of this tumor were not obtainable because, unfortunately, the tissue had dried out in storage.

Squamous cell carcinoma of the nipple was noted in 2 cases. In Figure 6, the section shows malignant squamous cells invading the dermis. Nothing is peculiar about squamous cell carcinomas of the nipple except, perhaps, the rarity of their occurrence in this particular location.

Figure 7 is another example of squamous cell carcinoma of the nipple illustrating the characteristic nests of epidermal cells. Epithelial pearls, which are characteristic of many of these tumors, are not well shown in either Figure 6 or Figure 7.

Basal cell carcinoma, present in 2 cases, is demonstrated in Figure 8. Islands and

strands of basal cells are shown growing down into the dermis to form nests. The central portion of this section shows pigmentation.

TREATMENT

In our series of 29 patients with 30 primary malignant lesions, 21 patients with adenocarcinoma underwent radical amputation and 4 simple amputation; 15 patients in this group received x-ray treatment after operation. The 1 patient having carcinomatous lesions in both breasts underwent simple amputation for each of them. X-ray treatment was used for the primary lesion in the right breast only. One of the 2 patients with squamous cell carcinoma had radical amputation and the other had a simple amputation. Both patients having basal cell carcinoma underwent simple amputation.

COMMENT

As mentioned previously, Fisher referred to a condition that he called "phantom tumor of the breast," manifested by discharge from the nipple but with no palpable tumor. In our series, 1 man had serous and bloody discharge of 1 year's duration with no palpable tumor or other manifestations of disease. Simple mastectomy revealed a papillary and comedo adenocarcinoma, grade 2, 5 millimeters in diameter in the right nipple. Eleven years later discharge exuded from the left nipple but no tumor could be palpated. Simple mastectomy demonstrated the presence of a papillary and comedo adenocarcinoma, grade 2, 0.6 centimeter in diameter, involving the left nipple.

Owen and co-authors wrote concerning occult carcinoma of the breast. In our series, 1 patient noticed a lump in the axilla as the first symptom. She later noticed an enlarged nipple and at operation a comedo and scirrhous carcinoma of the nipple, grade 3, was found. She died 1 year later with lumbar metastasis.

With the exception of the reports by these 2 authors, the literature is limited to isolated reports of cases with no uniformity of symptoms or physical findings.

FIG. 9. Case 16. Multicentric intraductal papillary carcinoma, grade 1, which possibly originated as benign florid papillomatosis, in a 50 year old white woman who gave a history of crusting and blood-tinged discharge from the nipple for 16 months. Hematoxylin and eosin, ×73.

These facts are mentioned because the lumps and indurations noted clinically in association with primary carcinoma of the nipple are so insignificant as to cause little concern to the examining physician. In this regard the contribution of Jones on benign florid papillomatosis of the nipple (Fig. 9) will serve a most useful purpose in directing attention to the nipple as a possible source of primary neoplasms.

Of our 29 patients with malignant lesions of the nipple, 1 had a retracted nipple as the only symptom, 1 had discharge from the nipple with slight crusting, and 1 had discharge from the nipple with slight retraction as the only symptoms; 3 patients had ulceration or eczema as the only sign. Pain was never a prominent symptom.

SUMMARY AND CONCLUSIONS

This series of 30 malignant lesions of the nipple occurring in 29 patients is too small to be statistically significant. A 5 year survival rate of 71.4 per cent, however, is at least suggestive that the early pathologic signs manifested by this lesion result in earlier and more effective treatment than is true of malignant lesions of the breast in general. Admittedly, this is a carefully selected series,

with no lesions more than 2.5 centimeters in diameter being included, which probably materially influences the 5 year survival rate.

Cancers of the nipple usually are of the same microscopic type and have the same prognosis as cancers of the breast. It should be noted that sarcoma, melanoma, or metastatic carcinoma did not occur in our series.

Any one of the symptoms of pain, retraction of the nipple, discharge of any kind, or change in the nipple such as eczema, ulceration, enlargement, or neoplastic formation should be considered to be malignant in origin until proved otherwise. The type of discharge from the nipple is not significant in determining the type of lesion present in the nipple or breast.

In malignant disease of the nipple, the average duration of symptoms of only 7.7 months, retraction of the nipple in nearly 50 per cent of the cases, pain in 30 per cent, ulceration or eczema of the nipple in 31 per cent, enlargement, tumor, or induration of the nipple in 69 per cent, and discharge from the nipple in 65 per cent of this series are all findings which, as a whole, are in marked contrast to those of ordinary carcinoma of the breast.

Treatment should consist of radical mastectomy, with or without postoperative roentgen radiation depending on the presence or absence of involved regional nodes and the preference of the surgeon.

In our series of cases, origin of the growths did not appear to originate in papillomas.

REFERENCES

1. Battle, W. H., and Maybury, B. C. Primary epithelioma of the nipple in a girl aged eleven. Lancet, Lond., 1913, 1: 1521–1522.
2. Cheatle, G. L., and Cutler, Max. Tumours of the Breast; Their Pathology, Symptoms, Diagnosis, and Treatment. London: Edward Arnold & Co., 1931.
3. Fisher, C. F. Tumors of breast producing discharge from nipple (phantom tumor of breast). West Virginia M. J., 1931, 27: 201–205.
4. Jones, D. B. Florid papillomatosis of the nipple ducts. Cancer, 1955, 8: 315–319.
5. Owen, H. W., Dockerty, M. B., and Gray, H. K. Occult carcinoma of the breast. Surg. Gyn. Obst., 1954, 98: 302–308.
6. Schreiner, B. F. Primary carcinoma of the nipple. Buffalo M. J., 1912–1913, 68: 509–512.

PARAPHARYNGEAL NEURILEMMOMA

DON O. GORE, M.D., ROBIN RANKOW, M.D., and
JOHN M. HANFORD, M.D., F.A.C.S., New York, New York

NEURILEMMOMAS of the parapharyngeal region are rare growths. The purpose of this article is to report 4 such cases seen recently at the Presbyterian Hospital in New York.

These tumors were first established as a pathologic entity by Verocay in 1910 (6, 7), but, as Guggenheim has pointed out, 2 cases were reported prior to this date in 1906 and 1907. Verocay originally termed these tumors neurinomas. Stout subsequently coined the term "neurilemoma," as being more accurate (5), and this has become the more commonly accepted designation, although many call them schwannomas.

Neurilemmomas are tumors of the neurilemma or nerve sheath of Schwann and histogenetically do not arise from the axis cylinder. These tumors are the most highly differentiated variant of Schwann cell tumors. They are either encapsulated by, or attached to the epineurium or perineurium. Some believe that they can always be enucleated and never involve the nerve diffusely. The involved nerve, therefore, does not course through the tumor but passes over or in the tumor capsule. During its growth, the tumor may push the nerve grossly to one side or may spread the nerve fasciculi apart.

Neurilemmomas are characteristically benign, slow growing, solitary tumors. Grossly, they are smooth, sometimes bosselated, encapsulated, soft, and gelatinous. They may be brown-gray, tan, or yellow in color and frequently are extremely vascular. When large, they may exhibit central hemorrhage, cystic degeneration, or liquefaction necrosis. Stout (5) believes that this latter characteristic distinguishes them from neurofibromas for which they are often mistaken.

From the Department of Surgery, Columbia University and the Surgical Service of the Presbyterian Hospital, New York.

Their size is variable; the smallest tumor excised from the head and neck area was reported as measuring 3 by 2 centimeters, while the largest extended from the mastoid process to the clavicle. They occur at almost any age but are most common in the third to sixth decades, equally in the sexes.

The microscopic features are fairly uniform and classical. There is a well defined connective tissue capsule. The tumor proper may be composed of one or both of the types of tissue described originally by Antoni.

Type A tissue consists of closely packed elongated spindle cells which resemble Schwann cells. These are arranged in an orderly manner, often in parallel series producing the typical "palisading effect." Sometimes the cells are arranged in streams or whorls (Verocay bodies) which resemble Wagner-Meissner tactile corpuscles. There are accompanying intercellular reticulin fibers which are rather straight and run parallel with the long axis of the tumor nuclei.

Type B tissue is more myxoid and consists of a loose network or Schwannian syncytium of anastomosing cells. These cells are variable in size and have long slender wavy processes. There are intercellular vacuoles with microcystic degeneration resulting from collagen degradation. Coalescence of the microcysts leads to grossly visible cavities. Also intercellular reticulin fibers and a variable amount of collagen are present.

The tumor may be extremely vascular and a frequent finding is thick collagen sheathing around the vessels occasionally with perivascular fibrosis and hyalinization. Neurites may be present in the tumor.

Neurilemmomas can occur in any cranial, sympathetic, or peripheral nerve but are commonest in the area of the head and neck.

TABLE I.—ANALYSIS OF 389 CASES OF NEURILEMMOMA AT THE PRESBYTERIAN HOSPITAL, NEW YORK, FROM JULY 1932 TO JULY 1955

	No.	*Per cent*
Tumors within the central nervous system		
1. a. Acoustic	228	90.8
b. Spinal cord	23	9.1
Total	251	64.6
2. Cases with multiple neurilemmomas	8	3.1
3. Cases with coincidental von Recklinghausen's disease	3	1.1
Tumors outside the central nervous system		
1. a. Head and neck	52	37.6
b. Upper extremity	41	29.7
c. Lower extremity	26	18.8
d. Chest	9	6.5
Mediastinum	7	5.1
Retroperitoneal	2	1.4
Lung	1	0.7
Total	138	35.4
2. Cases with multiple neurilemmomas*	7	5.1
3. Cases with coincidental von Recklinghausen's disease	3	2.1

*One of these cases had von Recklinghausen's disease as well.

The incidence in this location ranges from 26 to 43 per cent. The next most likely site is the anterior aspect of the upper extremities.

On reviewing the case records at this hospital, from 1932 to 1955, a similar type of distribution was found (Table I). Of a total of 389 cases of neurilemmomas, 64.6 per cent occurred within the central nervous system, while 35.4 per cent appeared outside of it. In the latter group, 37 per cent were above the clavicle and 29 per cent in the upper extremities. In this entire series only 4 cases were in the parapharyngeal area. These form the basis of this report.

A review of the available literature to date discloses a total of 47 case reports of parapharyngeal neurilemmomas, and fully two-thirds of these appear in the European literature. This article brings the published total to 51 such cases.

With respect to the parapharyngeal neurilemmomas, most of these arise from the vagus and the cervical sympathetic nerves. They lie in the posterior or vascular compartment of the parapharyngeal (pharyngomaxillary) space. From here they tend to expand into the retropharyngeal space where they may lose their encapsulated character by gradual fusion with the prevertebral musculature.

These are potentially dangerous tumors in that they may destroy tissue locally by expansion or pressure necrosis. They may also obstruct the esophagus, larynx, or carotid vessels. There are those who believe that interference with function of the nerve involved is characteristic of these tumors, while others are impressed with the rarity of this phenomenon.

When large enough to be symptomatic, awareness of a mass in the throat is the commonest complaint. Pain is decidedly uncommon. There may be hoarseness or dysphagia if the visceral efferent fibers of the vagus nerve are involved.

Weakness of the ipsilateral shoulder may indicate involvement of the spinal accessory nerve. Dyspnea is a late symptom in patients with bulky tumors, while ulceration and hemorrhage occur very late and are rarely encountered.

The pharyngeal component may be large enough to cause partial obstruction of the fauces or choanae.

On physical examination a nontender mass is palpable in the anterior cervical triangle or beneath the sternocleidomastoid muscle. It is slightly movable, fairly firm, and if very large, may feel cystic. It is not fixed to the overlying skin.

The internal carotid artery may be displaced anteriorly or medially and be palpable at the medial border of the tumor. Slaughter regards this finding, in conjunction with dysphagia and ipsilateral vocal cord palsy, as the diagnostic triad of this disease. Guggenheim believes that the internal carotid artery is rarely ever pushed medially, while Cutler stresses lateral displacement. The external carotid artery is frequently displaced laterally or anteriorly.

The upper limits of the tumor may be difficult to determine as these growths frequently extend to the base of the skull. A Horner's syndrome may be produced by the location of the tumor in, or by impingement upon, the perineurium of a sympathetic nerve, most notably the postganglionic fibers of the superior cervical ganglion. Such a finding

will persist postoperatively. More frequently, the Horner's syndrome occurs following surgery and is often permanent.

The pharyngeal wall may be seen to bulge at the tonsillar fossa or posterior lateral pharyngeal region, but the overlying mucous membrane is unattached and freely movable.

Laryngoscopy may reveal an ipsilateral vocal cord palsy. X-ray examination demonstrates only a nondescript soft tissue shadow. Lateral views may show an abnormal air pattern of the upper alimentary or air passage.

Differential diagnosis may be quite difficult. On a purely statistical basis, the most frequent cause of an asymmetric upper cervical enlargement in an adult is said to be involvement of lymph nodes secondary to an intraoral neoplasm. A diligent search, however, will disclose the primary lesion in such cases. The same may be said for a carcinoma of the nasopharynx or pharyngeal wall.

Branchial cysts are usually softer than neurilemmomas, more discrete, superficial, cystic, and rarely bulge into the pharynx.

Tumors of the retromandibular portion of the parotid gland may take the path of least resistance and expand toward the pharynx. For this reason they do not readily become evident as lateral upper cervical tumors and sialography may be of assistance in confirming the diagnosis.

Differentiation from lymphomas, reticulum cell sarcomas, or Hodgkin's disease may be hard, although in most instances these growths tend to be lobulated and rarely bulge into the pharynx.

Perhaps the 2 tumors from which differentiation may prove most difficult are neurofibromas and paraganglionic tumors. Of the latter, those arising from the carotid body seem to mimic most closely the picture presented by parapharyngeal neurilemmomas. They also are usually present in the upper lateral neck and often are asymptomatic. When large enough they may project toward the pharynx giving rise to dysphagia or hoarseness and a Horner's syndrome may be produced. However, they often present certain features, which, when present, serve to distinguish them from neurilemmomas.

Carotid body tumors occasionally have a thrill or audible bruit and may be compressible because of their extreme vascularity. This condition can sometimes be decreased by complete digital compression of the common carotid artery below which would not be true with a neurilemmoma.

While neurofibromas are said to be rarely limited to the neck and are usually associated with café au lait spots, we recently encountered a case at this hospital which was limited entirely to the neck and was not associated with abnormal pigmentation. This tumor was solitary, presented in the upper lateral cervical area, and caused a bulging of the pharyngeal wall. No Horner's syndrome, hoarseness, or dysphagia were present in this case, and the internal carotid artery was not displaced. Clinically, it was almost indistinguishable from the cases to be reported in this article, and the diagnosis of neurofibroma was only established by tissue section at operation.

Various authors have commented upon the coexistence of neurilemmomas with von Recklinghausen's disease. In 1946 Stout (5) reported, for example, that in 18 per cent of cases of solitary neurilemmomas, coexistent frank or suspected neurofibromatosis was also present. In our present series, we found this incidence to be only 1.5 per cent.

Another interesting finding in our survey was that a small number of patients had documented multiple neurilemmomas. One of these patients had 3 separate tumors and is reported herein as Case 2. Yet another patient had 3 separate neurilemmomas as well as von Recklinghausen's disease, well established by histologic study (see Table I).

Neurilemmomas are radioresistant tumors, and surgical excision is the treatment of choice. Prior to 1931 most parapharyngeal neurilemmomas were removed by the transoral route. This is no longer considered entirely safe or always satisfactory. The

same may be said for transoral biopsy. Incomplete removal, serious hemorrhage, or infection may follow this approach.

In our cases we found the external lateral cervical approach to provide safe and adequate access to these tumors. Precise anatomic identification of involved structures as well as complete removal of the tumor masses were possible. Frozen tissue sections established a positive diagnosis in each instance.

Ipsilateral vocal cord paralysis, anesthesia of the pharynx or larynx with regurgitation of food, cough, choking sensation, Horner's syndrome, dysphagia, shoulder weakness, and transient tachycardia have all been reported as postoperative complications. Only 1 death in the early postoperative period has been recorded.

It has been suggested that during the dissection a noninvolved segment of the nerve be identified on each side and traced back to the tumor mass. If enucleation of the tumor is not feasible, end-to-end anastomosis or a free nerve graft can be considered after excision of the mass. It might be said, parenthetically, that simple enucleation of the tumor from the nerve sheath is no guarantee against subsequent dysfunction of the involved nerve. It might also be pertinent to observe that the proximal portion of the involved nerve may be involved up to the base of the skull.

CASE REPORTS

CASE 1. L. S., a 36 year old white clerk, was admitted to Presbyterian Hospital on November 3, 1942. During the year preceding admission a slowly growing, painless mass developed in the right upper lateral neck. Apart from slight intermittent hoarseness he had been entirely asymptomatic. He gave a history compatible with rheumatic fever in childhood but this had never incapacitated him.

On admission, vital signs were entirely normal. He was a pale asthenic individual and the only notable findings were in the neck and chest. No Horner's syndrome was present and the pharynx was unremarkable. There was a firm, nontender, irregular, movable mass, 7 by 4 centimeters in size, under the upper third of the right sternocleidomastoid muscle. It was nonpulsatile. No enlarged cervical lymph nodes were palpable. His heart was enlarged to the left with a strong apical impulse, rhythm was regular, and a well localized blowing diastolic murmur was audible in the fourth left intercostal space.

Routine hemogram, urine analysis, Kline test, and electrocardiogram were unremarkable. X-ray films of the chest disclosed slight cardiomegaly, and roentgenograms of the neck were within normal limits, no abnormal calcification being present. During preoperative laryngoscopy some thickening of both vocal cords was seen, and there was an incomplete approximation of both cords in the anterior third but no paralysis was present. The preoperative impression was tuberculous cervical lymphadenitis.

On November 6, 1942 the right side of the neck was explored via an 8 centimeter oblique incision over the mass, below and behind the angle of the jaw. It was necessary to section the greater auricular nerve and external jugular vein to obtain adequate exposure. The tumor was ovoid, smooth, firm, discrete, and measured 4.5 by 3 by 2.5 centimeters. It displaced the internal jugular vein laterally and lay anterior to both the internal carotid artery and to the carotid bifurcation. The lower pole of the tumor ended just below the carotid bifurcation while the upper pole was situated quite near the base of the skull. The vagus nerve was identified at the lower pole but the upper attachment was rather diffuse, and the tumor had separated the nerve fascicles in this area. The main trunk of the vagus nerve below the tumor was divided and the upper pole freed upward by dividing the diffuse attachments. After removal, the upper pole of the tumor looked smooth and showed no sign of confluent nerve fibers tending to unite to form the main trunk of the upper part of the nerve. The superior laryngeal nerve which was partly attached to the tumor was dissected away from it.

The gross pathologic specimen consisted of an oval mass measuring 4.3 by 2.5 centimeters. It was completely covered by a thin fibrous capsule with a tag of firm white tissue at one pole (Fig. 1a). The mass was soft and on section was seen to be composed of a central core of moderately firm trabeculated white tissue and a periphery of mottled yellow tissue in which there were areas of hemorrhagic softening (Fig. 1b).

A well defined connective tissue capsule could be seen microscopically. The tumor consisted of compact fibrous tissue in which there were uniform spindle-shaped cells with uniform nuclei occasionally arranged in palisades. There were looser areas in which this arrangement was more irregular. These findings were characteristic of a benign neurilemmoma.

The diagnosis was neurilemmoma of the vagus nerve.

The immediate convalescent period was uneventful, and the patient was discharged on the sixth postoperative day. When next seen in the follow-up clinic 1 month later, his voice was weak and hoarse. He complained of a dry cough and a tendency to gag at breakfast. It was suspected that these symptoms

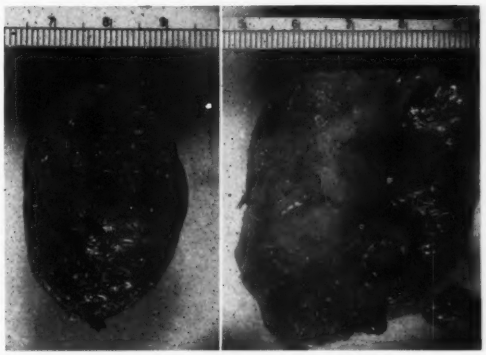
were largely due to a right vocal cord palsy, and on laryngoscopy this diagnosis was confirmed. He was followed at regular intervals for the next 8 years up to December 1950. His voice was still husky and he still gagged occasionally during meals. There was no local recurrence of the tumor and no Horner's syndrome.

CASE 2. F. M., a 55 year old white female clerk, was first seen at this hospital in 1945. She complained of choking sensations and sudden increase in size of a mass in the left side of the neck during the preceding fortnight. She gave a history of a small lump in the left upper neck of 2 years' duration. At that time she had also developed a sore throat and consulted a physician who found a mass within the throat.

When examined initially at this hospital, a large, left-sided, retropharyngeal tumor was noted. This mass was nontender, solid, and was thought to be continuous with a walnut-sized mass also present in the left submaxillary area. Stereoscopic x-ray films disclosed moderate osteoarthritic changes of the fifth cervical segment and a small cervical rib on the left. No abnormal calcifications were seen. The mass was aspirated transorally and smeared. No acid-fast bacilli were found. She refused admission to the hospital at this time.

The patient was next seen in September 1952 because of choking, dyspnea, and further increase in the size of the mass in the neck during the preceding 5 weeks. She agreed to admission for biopsy. Vital signs were normal. She was fairly obese, unco-operative, middle-aged, and with marked claustrophobia. She was not dyspneic, cyanotic, or edematous. Her voice was normal, as was her skin. No Horner's syndrome was present. Positive findings were confined to the head and neck region. There was a large mass occupying the posterior wall of the left oropharynx. It was smooth but lobulated, firm, nonpulsatile, nontender, and measured 6 by 3 centimeters. The overlying mucosa was normal. In the left upper lateral neck there were firm masses in the region of the upper deep cervical lymph nodes. The preoperative impression was carcinoma of the oropharynx with metastases to the upper cervical lymph nodes. A diagnosis of neurilemmoma was made after a transoral biopsy.

On October 7, 1952 under general anesthesia, the left lateral neck was explored. The tumor was approached through a 10 centimeter transverse incision at the level of the hyoid bone. The sternocleidomastoid muscle overlying the tumor was retracted posteriorly and a segment of internal jugular vein lying directly over the tumor was excised for exposure. Three separate tumor masses were encountered and each was mobilized from its nerve attachment. The uppermost arose from the vagus nerve at the level of the ganglion nodosum, the middle from the glossopharyngeal nerve, and the lowermost from a branch of the second cervical nerve. A definite encapsulation of each tumor made delivery rather easy, but the deep location of the most proximal tumor high in the neck at the base of the skull rendered this portion of the dissection difficult. The 3 tumors were approximately equal in size and lay adjacent to each other in the upper deep cervical region (Fig. 3a). The uppermost of these lay behind the oropharynx and caused a marked bulging of the pharyngeal mucosa.

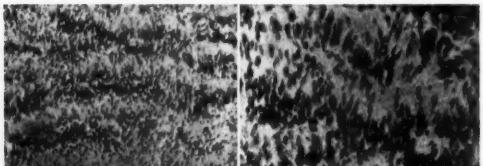


a b

FIG. 1. a, Gross specimen from Case 1. b, Cut surface of specimen.

The pathologic specimen consisted of 3 masses of tissue (Fig. 3a). Specimen No. 1, the most superior tumor, consisted of an irregularly lobulated fragment measuring 6 by 6 by 3 centimeters. There was a rough area labelled biopsy site and on the opposite side an area labelled vagus nerve attachment. The tissue was gray, moderately firm, and scattered yellowish areas were noted as well as firm lobulated gray zones. The mass was completely enclosed within a thin capsule and no cysts were seen. Specimen No. 2, labelled the middle tumor from the glossopharyngeal nerve, was similar to specimen No. 1. It measured 5 by 3 by 3 centimeters and at one edge a delicate filament was attached. At this attachment the nerve branched into fine strands which blended with the capsule of the tumor. Specimen No. 3, the lowermost tumor, consisted of a 6.5 by 3.5 by 3 centimeter mass completely enclosed within a thin capsule. One pole was labelled cervical nerve attachment. On section, this specimen was similar to the others and contained scattered punctate hemorrhages (Fig. 3b).

Microscopic sections of all 3 specimens showed a tumor of identical appearance. The tumor was surrounded peripherally by a well defined connective tissue capsule. The tumor proper consisted of lobules of spindle-shaped cells of uniform appearance oriented into extraordinarily well defined palisade formations. This solid type of tissue, the so-called Antoni type A, predominated; in occasional areas, there was a loose arrangement with a myxomatous stroma or Antoni type B tissue in which strands of spindle-shaped cells were scattered and small blood vessels presented thickened hyalinized walls (Fig. 2a and b).



a b

FIG. 2. a, Microscopic section from Case 2 demonstrating palisading characteristic of neurilemmoma. b, High power field demonstrating Antoni A type of tissue.

The diagnosis was multiple neurilemmomas of the cervical region.

The postoperative course was complicated by bronchopneumonia which developed over the first 3 postoperative days. A Horner's syndrome appeared immediately and a paralysis of the left vocal cord and dysphagia were also evident. She was followed at intervals, and when last seen on April 22, 1955, three years after operation, her swallowing and voice had greatly improved. A Horner's syndrome persisted as did the paralysis of the left side of the tongue and hoarseness; but she was pleased about her great improvement in speech, voice, and swallowing. The tumors have not recurred.

CASE 3. P. H., a 34 year old white executive, was admitted to this hospital on March 23, 1955. Five months previously he had developed a painless lump in the right upper neck. This had not increased noticeably in size. In January 1955, he consulted a doctor who administered antibiotics for 2 weeks and performed a tonsillectomy. A pharyngeal mass persisted on the right. In the 3 weeks preceding admission he also observed a slight weakness of the lower part of the face on the right side with tearing of the right eye. He denied any dysphagia, dysphonia, cough, fever, syncope, or night sweats. The mass in the neck was never tender.

When admitted, vital signs were found to be normal. His voice was normal, and he was not dyspneic. A right Horner's syndrome was present. There was slight weakness of the right orbicularis oris but no other abnormalities of the seventh cranial nerve were present. The neurologic examination was otherwise within normal limits. Beneath the angle of the mandible on the right there was a vaguely outlined mass 6 by 4 centimeters. It was anterior to the sternocleidomastoid muscle, moderately firm but slightly cystic on bimanual palpation, and was fixed and nontender. No thrill or bruit was detectable. The mass could not be transilluminated. The tumor was palpably continuous with an egg-sized mass in the right lateral pharyngeal wall, extending from the oropharynx into the nasopharynx. The overlying mucous membrane was normal. X-ray films in various projections of the mandible and cervical spine were taken. These disclosed normal osseous structures and a suggestion of a soft tissue mass in the right submandibular area near the angle of the mandible. Preoperative laryngoscopy disclosed normally functioning vocal cords. In the differential diagnosis, branchial cyst, carotid body tumor, and parotid neoplasm were considered.

On March 23, 1955, under general anesthesia with nasoendotracheal intubation, the right side of the neck was explored. A transverse incision was made along the skin lines in the upper lateral neck from the right mastoid toward the midline. The platysma was divided and the cervical fascia opened vertically. The carotid arteries were freed from the overlying tumor at the level of the bifurcation. A frozen section biopsy diagnosis of neurilemmoma was made. The dissection was then started at the lower pole, where there was a thick capsule. The tumor was situated between and posterior to the carotid vessels above the bifurcation, displacing the internal carotid artery medially. The tumor arose from the vagus nerve from which it was enucleated. During this process the nerve was shredded but left in continuity. The neurilemmoma extended to the base of the skull and in this location the capsule fused with the prevertebral fascia making the dissection tedious.

The gross pathologic specimen consisted of an oval, flattened mass of pinkish-yellow tissue with a fine loose areolar capsule. It weighed 48 grams and measured 6.5 by 5 by 1.5 centimeters (Fig. 4a). On section the surface bulged and was yellow-gray and lobulated. A few areas of hemorrhage were present (Fig. 4b).

Microscopic sections showed an interlacing network of wavy, flowing streams of cells with areas of palisading. In the stroma a few fat cells and a moderate number of blood vessels were noted. The periphery of the tumor showed a zone of compression of fibrocytes simulating a capsule.

The diagnosis was neurilemmoma of the cervical region.

Convalescence was smooth. There was a very mild transient paresis of the hypoglossal nerve which disappeared by the third postoperative day. There was no hoarseness but the patient complained of dysphagia and some regurgitation. Laryngoscopy on the sixth postoperative day revealed edema and suggillation of the right pharyngeal wall. On the eleventh postoperative day, mild paresis of the right vocal cord was noted with regression of the pharyngeal edema. The Horner's syndrome on the right noted preoperatively persisted. In the follow-up period the patient reported severe pain on swallowing. This was associated with an intense pain radiating to the right ear. These

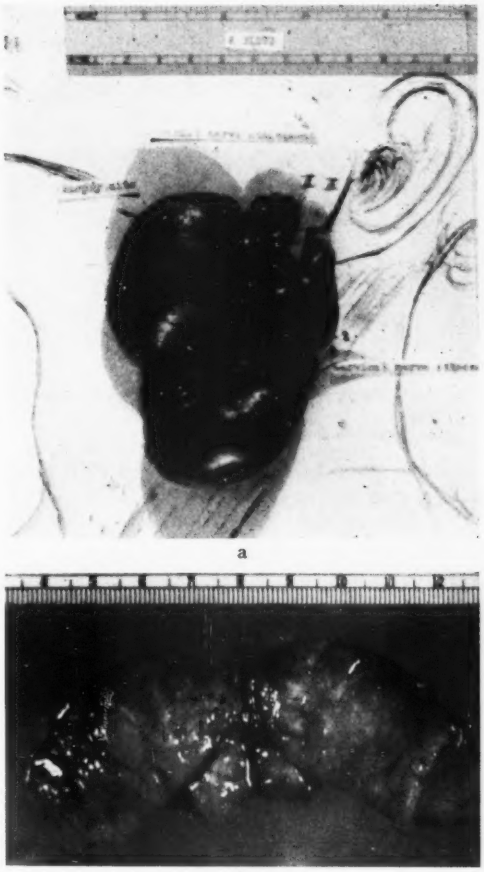
symptoms slowly subsided. It was believed that these difficulties might be related to sectioning of the sensory superior laryngeal branch of the vagus nerve as it passes behind the internal carotid artery. The patient was last seen in September 1955, six months postoperatively. At this time the Horner's syndrome as well as the vocal cord paresis were still present. The swallowing difficulties had virtually disappeared. There was no recurrence of the tumor.

CASE 4. W. K., A 36 year old white housewife, was admitted to this hospital on May 4, 1955. In April 1955 the patient had noticed a small swelling below the lobule of the left ear. This had increased slowly in size and was nontender. Shortly before admission the patient was laryngoscoped because of persistent hoarseness but no abnormalities of the vocal cords were seen. X-ray films of the neck and skull taken at this time were also normal. She had mild diabetes mellitus which was easily controlled by diet.

Vital signs on admission were normal. She was slightly built but well developed and with normal skin. She was hoarse but no Horner's syndrome was present. A mass was present along the anterior border of the upper portion of the left sternocleidomastoid muscle but the overlying skin was normal and freely movable. The mass was approximately 6 by 3 centimeters, firm, smooth, nontender, nonpulsatile, and felt fixed. No distinct carotid pulsation could be felt medially. The lower pole of the mass ended in a vague nodule 1.5 centimeters in diameter. The upper limits of the tumor could not be accurately determined under the angle of the mandible. The left oropharyngeal wall was noted to be bulging, but the overlying mucous membrane was normal. Fasting blood sugar was 91 milligrams per cent. Routine urine analysis and hemogram were normal. Because of our recent experience with these tumors, parapharyngeal neurilemmoma was considered in the preoperative differential diagnosis, together with mixed tumor of the parotid and cervical lymphadenopathy.

Operation was performed on May 15, 1955 under general anesthesia with nasoendotracheal intubation. An upper left cervical incision was made along a skin line. The tumor was located anterior to the internal carotid artery and had displaced it medially. The external carotid artery was pushed anteriorly. The internal jugular vein was displaced posteriorly. The tumor extended from just below the level of the carotid bifurcation toward the pharynx, the lateral wall of which bulged at the tonsil. Its upper pole ended at the level of the hypoglossal nerve. This tumor arose from the vagus nerve, the fibers of which were spread out over it. It was fairly simple to shell it out of its capsule, leaving the fibers of the nerve apparently intact. It is of interest that a slender twig could be traced into the tumor from the hypoglossal nerve also.

The gross pathologic specimen consisted of an encapsulated, ovoid, slightly bossellated mass. It was mottled yellow to tan-white, rubbery, and foci of subcapsular hemorrhage were evident. It weighed 14 grams and measured 4.2 by 2.7 by 2.2 centimeters (Fig. 5a). On section the cut surface was mottled yellow and tan-white. The yellow areas were translucent and gelatinous while the semiopaque tan-white areas had a whorl-like appearance (Fig. 5b).

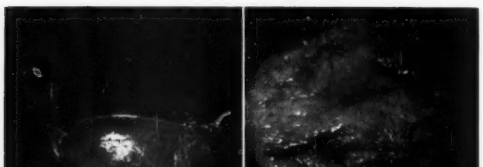


a

b

FIG. 3. a, Gross specimen from Case 2. b, Cut surface of specimen of vagal component.

Microscopic sections showed an encapsulated tumor composed of 2 types of tissue. In most areas the tumor was compact and made up of spindle-shaped cells with uniform elongated nuclei arranged in parallel rows. Collagen intervening between these cells was variable; being abundant and somewhat hyalinized in zones between rows of nuclei. Occasional areas were loose-textured and composed of spindle-shaped cells without the above orderly arrangement. A moderate number of capillary-sized blood vessels with heavy collagen walls were noted. Occasional inflammatory cells appeared in the loose-textured areas.



a b

FIG. 4. a, Gross specimen from Case 3. b, Cut surface of specimen.

Scattered throughout were small pools of protein precipitate as well as foci of recent hemorrhage.

The diagnosis was neurilemmoma of the cervical region.

During the first 24 hours postoperatively, there was a very mild hypoglossal nerve palsy which cleared in the following 2 days. Weakness was also noted in the mandibular branch of the facial nerve for the first 2 weeks, then disappeared. Hoarseness persisted, and some dysphagia with gagging and regurgitation developed, but no Horner's syndrome developed. Laryngoscopy disclosed marked left vocal cord palsy. Cystitis flared up postoperatively and was a distressing problem. When seen in December 1955, seven months after operation, she still suffered from sudden attacks of choking and cough often unrelated to eating, due presumably to collection of mucus and saliva in the partly anesthetic larynx and also to the palsied vocal cord. The quality of the voice, however, was definitely improved and there was no recurrence of the tumor.

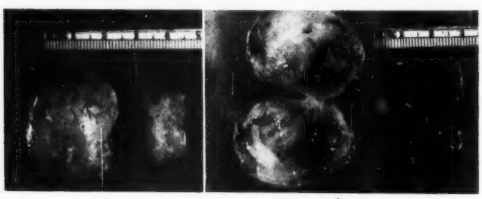
COMMENT

Although neurilemmomas are commonest in the head and neck areas, they are rarely encountered in the parapharyngeal region. In this location they arise most usually from the vagus or cervical sympathetic nerves. The importance of these tumors lies chiefly in their location, where they may give rise to compression of adjacent vital structures or be mistaken for malignant tumors. The differential diagnosis of a firm, painless mass in the upper lateral neck with associated bulging of the posterior lateral pharyngeal wall can be difficult. Neurilemmoma should be strongly considered if there is medial displacement of the internal carotid artery as well as dysphagia and hoarseness.

Surgical exploration with frozen tissue section is recommended. A lateral cervical approach under endotracheally administered anesthesia permits an anatomic dissection of these tumors, and complete removal is usually possible. The most frequent postoperative complications are vocal cord paralysis with hoarseness, cough and choking attacks, Horner's syndrome, and facial or hypoglossal nerve weakness. The paresis from dysfunction of the mandibular branch of the facial nerve and that from the hypoglossal are almost always mild and transient. While hoarseness may be transitory, the Horner's syndrome is frequently permanent. The cough and choking attacks may be due to superior laryngeal nerve damage as well as to vocal cord paralysis. Compensation and readjustment to these unpleasant symptoms may be slow and rarely is complete.

Total excision is usually possible but partial resection may be advisable in rare cases if irreparable damage to the vagus nerve is to be avoided or minimized. It seems unlikely that nerve suture or graft of the vagus would provide the patient with functioning inferior or superior laryngeal nerves.

There are remote instances of multiple neurilemmomas in the neck. One of the cases reported here is of this category and is of unusual interest in that there were 3 separate neurilemmomas present in the upper neck, each arising from a different nerve, 1 of them being parapharyngeal in its location.



a b

FIG. 5. a, Gross specimen from Case 4. Lymph node removed incidentally shown at right. b, Cut surface of specimen.

The occurrence of von Recklinghausen's disease coincident with neurilemmoma was found to be only 1.5 per cent. Reference is made to a case in which not only multiple neurilemmomas were present but also von Recklinghausen's disease.

SUMMARY

1. This study confirms the findings of other investigators as to the preponderant incidence of neurilemmomas in the head and neck. Exclusive of the central nervous system, the actual incidence in this series of 389 cases was 37 per cent, or higher than anywhere else in the body.

2. Four cases of neurilemmoma of the parapharyngeal region are presented, bringing the total number of reported cases to 51.

3. The clinical features are described and the gross and microscopic pathology are reviewed.

4. Surgical excision is the only known treatment, and an external lateral cervical approach provides adequate and safe access to these tumors.

5. Temporary and permanent postoperative sequellae are discussed.

REFERENCES

1. Antoni, N. R. E. Ueber Rueckensmarkstumoren und Neurofibrome Studien zur pathologischen Anatomie und Embryogenese mit einen klinischen Anhang. Munchen: J. F. Bergmann, 1920.
2. Cutler, E., and Gross, R. Neurofibroma and neurofibrosarcoma of peripheral nerves. Arch. Surg., 1936, 33: 733–779.
3. Guggenheim, P. Schwannoma of the pharynx. J. Internat Coll. Surgeons, 1953, 19 (4): 450–474.
4. Stout, A. P. The peripheral manifestations of the specific nerve sheath tumor (neurilemoma). Am. J. Cancer, 1935, 24: 751-796.
5. Idem. Neurofibroma and neurilemoma. Clin. Proc., Cape Town, 1946, 5: 1–12.
6. Verocay, J. Multiple Geschwulste als systemerkrankung am nervosen Apparate. Festschrift f. Chiari. Pp. 378–415. Wien and Leipzig: W. Braunmüller, 1908.
7. Idem. Zur Kenntnis der Neurofibrome. Beitr. path. Anat., 1910, 48: 1–169.

THE EXPERIMENTAL PRODUCTION OF THE PULMONARY EMBOLISM SYNDROME AND THE EFFECTS OF VARIATIONS OF SYSTEMIC ARTERIAL PRESSURE ON ITS COURSE

DAVID STATE, M.D., Ph.D., F.A.C.S., and PETER F. SALISBURY, M.D., Ph.D.,
Los Angeles, California

PULMONARY EMBOLISM continues to claim many lives annually. A number of divergent theories have been proposed to explain the symptoms and mode of death attending this condition, but until the exact sequence of physiologic events following pulmonary embolization is more clearly understood little progress can be expected in the therapeutic approach to this problem.

Study of the functional changes following pulmonary embolization in man has been hampered by the lack of an experimental procedure in animals which would closely resemble the clinical syndrome of pulmonary embolism. Our purpose is to present a technique for producing pulmonary embolization in dogs and to describe the effects of variations of the systemic arterial pressure upon its production and course.

METHODS

Mongrel dogs were deeply anesthetized with intravenous pentobarbital sodium, 25 milligrams per kilogram. Five dogs were kept lightly anesthetized with a slow intravenous infusion of 0.3 per cent thiamylal sodium (surital®); the results of the two types of anesthesia were identical. The animals were then given heparin, 1 milligram per kilogram. Pressure sensing plastic cannulas were inserted into the femoral artery through the right jugular vein into the right ventricle. Pressures were recorded on Statham pressure transducers, model P 23A, amplified with Edin carrier amplifiers, model 8810, and registered on Edin direct-writing multichannel oscillograph, model 8066. In a number of experiments, 0.075 inch outside dimension polyethylene catheters were also inserted into tertiary branches of the right and left pulmonary arteries and pressures were recorded on Statham pressure transducers, model P23B, and amplified and recorded as described.

Under endotracheal positive-pressure respiration, the chest was entered via a transverse sternum-splitting incision at the level of the fourth intercostal space. The pericardium was incised, and the pulmonary artery and its right and left branches were identified and isolated.

Embolization was produced with two different methods. In method 1, a sphere approximately equal in diameter to that of the main pulmonary artery was selected from a series of solid methyl methacrylate (lucite) spheres of progressively increasing diameters ($\frac{2}{8}$, $\frac{3}{8}$, $\frac{4}{8}$, $\frac{5}{8}$, $\frac{6}{8}$ inch). An incision was then made into the tip of the right auricular appendage; the walls of the appendage were grasped and held apart with 3 or 4 hemostats and the lucite sphere was inserted into the right arium. The auricular appendage was then closed with a noncrushing clamp. The plastic sphere was

From the Department of Surgery and the Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles.
This study was supported in part by Grant No. H-1986 from the National Heart Institutes, U. S. Public Health Service to Dr. D. State, Grant No. H-1158 from the National Heart Institutes, U. S. Public Health Service to Dr. P. Salisbury and a grant from the Los Angeles County Heart Association.

pushed gently from the right atrium into the right ventricle and the pulmonary artery. Its progress could be observed visually and by palpation. It was possible to withdraw and to reinsert the plastic sphere a number of times and to note the effects of such repeated embolization.

Method 2 for the production of embolism was the insertion of a balloon-tip catheter into the pulmonary artery. The catheters described by Dotter and Lukas and Agress were used for this purpose. The Dotter-Lukas catheter was introduced through the jugular vein, the Agress catheter through a stab wound in the right ventricle which was controlled with a purse-string suture. The occlusion or patency of the main, or right and left pulmonary arteries were monitored by changes of the pressure in the tertiary branches of the pulmonary artery.

In this preparation blood pressure changes were effected by altering the blood volume. Blood was withdrawn from the animal or added to the animal, either through the same cannulas which were used for pressure registration purposes or else through a reservoir filled with heparinized blood, which could be raised or lowered at will, and which was connected with the carotid artery. Injections of phenylephrine hydrochloride (neosynephrine®) were made through the catheter in the right ventricle.

RESULTS

In the course of this investigation it became apparent that the level of the systemic arterial pressure at the time of embolization was of the utmost importance in determining the consequences of embolization. Our experimental results are, therefore, divided into two groups: embolization in "normotensive" (systolic arterial pressure in excess of 75 mm. Hg) dogs and embolization in "hypotensive" (systolic arterial pressure less than 75 mm. Hg) dogs.

Pulmonary embolization in normotensive dogs. In 26 observations on 24 dogs with a systolic arterial pressure exceeding 75 millimeters of mercury, pulmonary embolism was produced as described. The emboli moved through the infundibulum and into the pulmonary artery with a to-and-fro motion which was simultaneous with the contractions of the heart. The backward phase of this motion coincided with diastole. As soon as the sphere was lodged, or as soon as the balloon was filled with a certain definite volume of water which varied from dog to dog, pressures in the tertiary branches of the pulmonary artery, distal to the occlusion, reflected the degree of obstruction of the main pulmonary vessels (Figs. 1 and 2). An increase of the right ventricular systolic pressure followed occlusion. The right ventricle became markedly dilated. The pulmonary artery proximal to the embolus showed pronounced dilatation. At the same time the systemic arterial pressure fell. As the pressure in the right ventricle increased, the pulmonary artery became distended to a point where the embolus moved to the bifurcation and blood flowed past the obstructing embolus which occupied only a part of the lumen of the dilated pulmonary artery. At this point, the systemic arterial pressure rose and often returned to the pre-embolization level. When the systemic arterial pressure returned to normal levels, the embolism was often lodged at the bifurcation of the main stem pulmonary artery or within one of the primary major divisions, prohibiting blood flow to one lung but permitting flow through the other.

In most instances when the pre-embolization systemic arterial systolic pressure was over 120 millimeters of mercury, the lodgment of the embolus resulted in a lowering of the arterial pressure for a few seconds only. When the systemic arterial pressure was between 75 and 120 millimeters of mercury at the start of the experiment, embolization caused a more prolonged decrease of the arterial pressure which usually, but not always, returned to the previous level within a few minutes. The 24 normotensive dogs survived acute embolization until they were sacrificed at the completion of the experiment.

The systolic pressure generated by the right ventricle after obstruction of the pulmonary artery of normotensive dogs reached a maximum of 140 millimeters of mercury. The end-diastolic pressure of the right ventricle was not elevated after embolization of dogs with a systolic peripheral arterial pressure over 100 millimeters of mercury. With peripheral arterial systolic pressures between 75 and 100 millimeters of mercury the right ventricular end-diastolic pressure often rose to zero indicating some degree of decompensation of the right ventricle.

Pulmonary embolization of hypotensive dogs. In 25 observations on 14 dogs, the arterial systolic pressure was lowered to a level of less than 70 millimeters of mercury by variation of the blood volume.

In this series the lodgment of the embolus or occlusive distention of the balloon in the main pulmonary artery was followed by an immediate, progressive fall of the systemic arterial pressure, which eventually reached levels of 10 to 15 millimeters of mercury and was followed by ventricular fibrillation and death (Fig. 3). After lodgment of the embolus in this group of dogs, the myocardium became cyanotic, the right ventricle remained dilated in systole, and its contractions were feeble and ineffective. The right ventricular systolic pressure rose to a maximum of 30 millimeters of mercury but this was not sufficient to dilate the pulmonary artery enough to permit blood flow through it. Within 20 to 30 seconds after embolization, right ventricular systolic pressure commenced to decline. The right ventricular end-diastolic pressure showed a pronounced increase after embolization, indicating severe decompensation of the right ventricle. In 14 of the 25 observations reported here, resuscitating therapeutic measures were not employed and the animals died in the manner which has been described.

Resuscitation of hypotensive dogs with pulmonary embolism. In 12 dogs with hypotension, death from pulmonary embolism was considered imminent because of "complete incompetence" of the circulation indicated by progressively falling systemic pressure (to 15 mm. Hg), rising right ventricular end-diastolic pressure, and falling right ventricular systolic pressure. Previous experiments had shown that, when this hemodynamic state had supervened, the embolized dogs would not recover spontaneously. When the dogs with complete incompetence were treated with blood infusion into the carotid artery by raising the arterial reservoir, or with intracardiac injection of 2 milligrams of neosynephrine combined with cardiac massage, it was possible to restore normal systemic arterial pressure as well as normal right ventricular end-diastolic pressure (Fig. 4). The right ventricular systolic pressure remained elevated after resuscitation. The resuscitated animals survived until they were sacrificed deliberately. Expansion of the blood volume by intravenous infusion of blood was completely ineffective in this situation.

DISCUSSION

It has been clearly demonstrated that the syndrome of severe acute pulmonary embolism in man is characterized by shock co-existing with decompensation of the right ventricle, as indicated by direct pressure measurements and by electrocardiographic data. Animal experiments which are intended to duplicate the clinical syndrome of pulmonary embolism in man must repeat the cardinal features of this entity.

In humans the syndrome is usually caused by a large embolus which occludes one of the major pulmonary arteries. Reproduction of the pulmonary embolism syndrome in dogs has been attempted utilizing injections of air or suspension of small particles. These types of embolization are not comparable to that seen in man. When large emboli have been used in animals with intact chests, their diameter has been determined by the size of the peripheral veins. The position of the embolus and the degree of obstruction of the pulmonary arteries which was produced have been variable and difficult to assess.

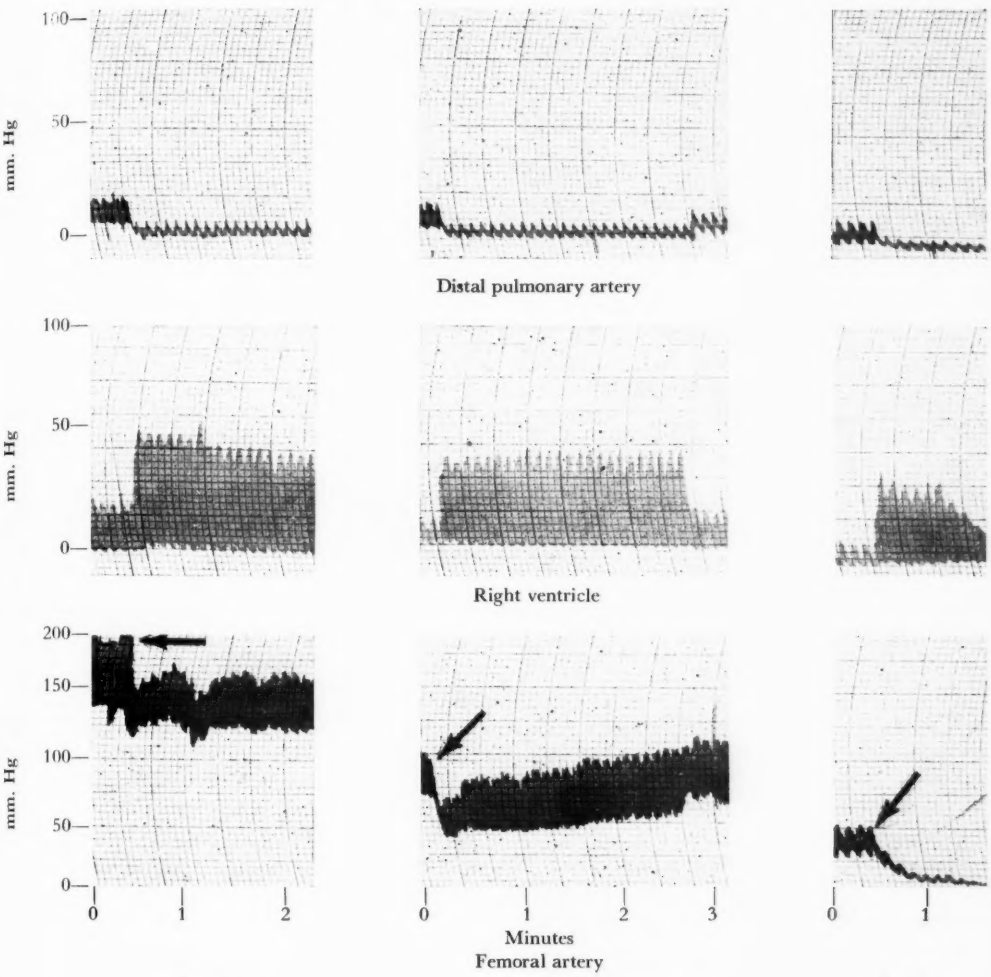


FIG. 1. FIG. 2. FIG. 3.

FIG. 1. Effect of sudden embolization of main pulmonary artery in hypertensive dog. Balloon in the pulmonary artery distended with 3.5 milliliters of water at arrow. Note the pulmonary artery pressure distal to the embolus drops to zero, indicating a complete obstruction. The right ventricular pressure rises and remains elevated. The systemic arterial pressure falls from 200 to approximately 160 millimeters of mercury.

FIG. 2. Effect of sudden obstruction of main pulmonary artery in normotensive dog. Calibration and tracings as before. Pulmonary artery balloon distended with 3.0 milliliters of water at arrow (same dog as Fig. 1). Note the more prolonged decrease in systemic arterial pressure which, however, gradually returns to pre-embolization levels. The return of the pressure in the distal pulmonary artery and right ventricle to normal levels at approximately the 3 minute mark was due to deflation of the balloon in the pulmonary artery.

FIG. 3. Effect of sudden obstruction of main pulmonary artery in hypotensive dog. Calibration and tracings as before. Pulmonary artery balloon is distended with 3.0 milliliters of water at arrow (same dog as Fig. 2). The distal pulmonary artery pressure dropped to zero. The right ventricular pressure rose to 30 millimeters of mercury but within 30 seconds the pressure started to decline. The femoral artery pressure dropped from an initial systolic pressure of 50 to from 10 to 15 millimeters of mercury. At this point ventricular fibrillation appeared.

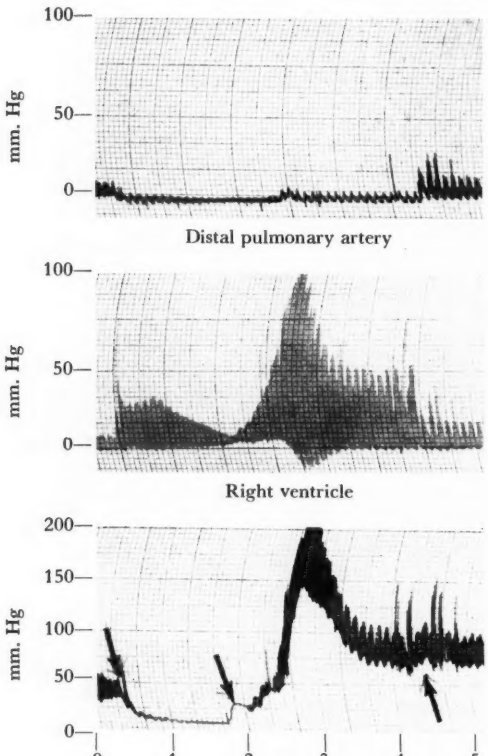


FIG. 4. Resuscitating effect of elevating systemic arterial pressure on complete incompetence of right ventricle following pulmonary artery obstruction in the hypotensive dog. Calibration and tracings as before. Pulmonary artery balloon is distended with 3.0 milliliters of water at left arrow. Arterial pressure reservoir is opened and elevated 150 centimeters above dog at middle arrow. One hundred seventy-five milliliters of blood flowed from the reservoir into the dog in 2 minutes. Balloon is deflated and reservoir disconnected at right arrow. The pulmonary artery balloon remains distended with 3.0 milliliters of water before and after elevation of systemic arterial pressure. Note that as systemic arterial pressure is raised, the right ventricular pressure becomes elevated, and the distal pulmonary artery pressure is also increased, indicating flow of blood beyond the obstructing embolus. This animal survived.

The experiments reported here resulted in controlled massive embolization of the canine pulmonary artery which started a train of physiologic events comparable to those seen in man with massive pulmonary embolization.

The graded size, plastic ball technique and the controlled distensible bag have certain advantages and disadvantages. In favor of their use are the facts that one can select an embolus of known and unvarying size, which is capable of assured blockage of the main pulmonary artery or of its right or left main branches, as desired. The embolus can be seen and palpated so that no doubt exists as to its position. Furthermore, it can be dislodged and withdrawn, giving repetitive opportunities to study the effect of obstruction of the pulmonary arteries. The disadvantage lies in the fact that this type of experiment must be performed in the fully anesthetized open-chest dog, in which circulatory reflexes and the other influences of the nervous system are not easy to observe, in which positive pressure respiration is usually necessary, and in which relations within the pulmonary circuit are changed from normal. The Dotter-Lukas balloon catheter has the added disadvantage of obstructing the pulmonary artery in a manner not easily regulated. One-tenth milliliter change in balloon volume often makes the difference between total obstruction and some degree of patency of the vessel.

In the present experiments the characteristic picture of lethal sudden pulmonary embolism in man was reproduced in the dog, by lowering its systemic arterial pressure to a critical value. The experimental findings in these experiments would seem to substantiate the hemodynamic mechanism of death in massive pulmonary embolization so ably postulated by Megibow, Katz, and Steinitz. The right ventricular systolic pressure rose after lodgment of the pulmonary embolus even as the systemic arterial pressure was falling precipitously. The right ventricular end-diastolic pressure rose, indicating decompensation. As was previously observed by one of us (6), right ventricular contractile strength in anesthetized dogs is directly related to the systemic arterial pressure. Elevated arterial pressure multiplies right ventricular strength by virtue of the resultant augmentation of the

coronary flow. Reversal of the catastrophic course of experimental pulmonary embolism was possible in our experiments only when the arterial pressure was raised.

In unpublished experiments from our laboratory, it was found that the pulmonary artery pressure of dogs rises and falls parallel with variation of the systemic arterial pressures. It is not known whether or not this situation exists in the human, but there is no evidence to the contrary. It is believed that in clinical pulmonary embolism the attention of the physician should not be focused primarily upon the pulmonary vascular resistance and the factors which influence it. The augmentation of right ventricular strength which occurs as a result of increased peripheral arterial pressure greatly exceeds the relatively slight elevation of pulmonary resistance which always seems to accompany increased peripheral arterial pressure.

In our experiments the mechanism of recovery from otherwise lethal pulmonary embolism was concerned exclusively with the contractile strength of the right ventricle. When life was maintained even with a very large plastic sphere in the pulmonary artery, the compensated right ventricle either dilated the pulmonary artery to a point where sufficient blood flowed around the obstructing material, or else the embolus was pushed wholly, or in part, past the bifurcation and into one of the two branches of the pulmonary artery, permitting adequate blood flow through the other branch.

The clinical implications of these experiments are worthy of note, even though our experiments provide information only on mechanisms in massive pulmonary embolization but not in those cases in which death follows embolization of isolated secondary or tertiary branches of the pulmonary artery. It has been the common experience that lethal pulmonary embolism occurs with particular predilection in those patients who are beginning to ambulate after prolonged recumbency and in whom postural hypotensive states may exist, as well as in patients with cardiac decompensation. We believe the preferred mode of therapy in patients with pulmonary embolism should be directed toward maintaining systemic arterial pressure with pressor agents given in adequate amounts. Recent reports by De Swiet and Wolff have indicated the value of pressor agents in 3 patients with pulmonary embolism; such agents must be given in very large amount in order to be effective; in 1 patient a total of 798 milligrams of levarterenol (levophed®) was used over a period of several days.

The clinical syndrome of pulmonary embolism must be influenced by many variables of which hemodynamic factors constitute only one aspect. There may be other factors which remain to be studied experimentally and which may modify the experimental pulmonary embolism syndrome observed in the dog, i.e., pre-existing pulmonary hypertension, hypoxia, acidosis, and levels of circulating steroid hormone. Recent studies by Comroe and Smith and their associates would indicate that certain humoral agents (serotonin) may be liberated from the clotted blood and be responsible for certain symptoms associated with pulmonary emboli. It is believed that such humoral agents are at best only ancillary factors in the clinical syndrome of pulmonary embolism because of their transient effects and also inasmuch as blood clots of large volume often occur in other parts of the body where they could be expected to form identical substances but do not give rise to the characteristic picture of pulmonary embolism.

SUMMARY

1. In open chest anesthetized dogs, pressures were registered in the femoral artery, the right ventricle, and left or right tertiary branches of the pulmonary arteries. Graded plastic spheres or distensible balloons were inserted into the pulmonary artery.

2. A hemodynamic syndrome was produced which closely resembled massive pulmonary embolism in man. Embolism was uniformly fatal in hypotensive, hypovolemic

dogs. Comparable embolization was not fatal in normotensive animals, irrespective of their blood volume. Embolized dogs with complete decompensation of the right ventricle and with total collapse of the peripheral arterial pressure could be rescued only by therapeutic maneuvers which effectively elevated the systemic arterial pressure, whether or not the blood volume was increased.

3. Survival of dogs after massive pulmonary embolism depends upon a right ventricle capable of generating sufficient contractile strength to impact the embolism at the bifurcation and to dilate the pulmonary artery so as to permit blood flow past the embolism. The role of peripheral systemic pressure as a primary factor in determining the maximum contractile strength of the right ventricle is again confirmed.

REFERENCES

1. Agress, C. M., Rosenberg, M. J., Jacobs, H. I., Binder, M. J., Schneiderman, A., and Clark, W. G. Protracted shock in the closed-chest dog following coronary embolization with graded microspheres. Am. J. Physiol., 1952, 170: 536–549.
2. Comroe, J. H., Van Lingen, B., Stroud, R. C., and Roncoroni, A. Reflex and direct cardiopulmonary effects of 5-OH-tryptamine (serotonin). Am. J Physiol., 1953, 173: 379–386.
3. De Swiet, J. The use of l-noradrenalin in the treatment of acute cor pulmonale. Brit. M. J., 1955, 2: 1253–1254.
4. Dotter, C. T., and Lukas, D. S. Acute cor pulmonale; an experimental study utilizing a special cardiac catheter. Am. J. Physiol., 1951, 164: 254–262.
5. Megibow, R. S., Katz, L. N., and Steinitz, F. S. Dynamic changes in experimental pulmonary embolism. Surgery, 1943, 11: 19–32.
6. Salisbury, P. F. Coronary artery pressure and strength of right ventricular contraction. Circulation Res., 1955, 3: 633–638.
7. Smith, G., and Smith, A. N. The role of serotonin in experimental pulmonary embolism. Surg. Gyn. Obst., 1955, 101: 691–700.
8. Wolff, F. W. Shock due to pulmonary embolism; treatment with l-noradrenalin. Lancet, Lond., 1954, 267: 72–73.

THE CHARACTERISTICS OF REGENERATION OF RESPIRATORY EPITHELIUM

NOBLE O. CORRELL, JR., M.D., and EDWARD J. BEATTIE, JR., M.D., F.A.C.S.,
Chicago, Illinois

THERE IS EVIDENCE of considerable interest in the repair of defects of the trachea and bronchi. Ideally, the reconstructed area should have the same resiliency as the remainder of the wall, be airtight, maintain a lumen, and should be lined with respiratory epithelium. A study of the regenerative characteristics of tracheobronchial epithelium, therefore, seems in order.

REVIEW OF THE LITERATURE

Proetz (5), in 1941, disclosed many of the secrets of the mucosa of the paranasal sinuses. Such tissue is similar to the epithelium which lines the tracheobronchial tree.

Knowlton and McGregor studied the regeneration of the epithelium of the maxillary sinus of the dog. They found that the regenerated epithelium was well established after 1 month and completely regenerated in 2 months.

A record of the gradual return to normal of newly regenerated epithelium in the human maxillary sinus was made by Gorham and Bacher 26 years ago. Latta and Schall found that the ciliated mucosa developed from cuboidal undifferentiated basal cells which are quite resistant to adverse environmental conditions. These investigators also found that acute irritation caused the epithelial lining of the sinuses to become more heavily ciliated. Proetz (4) has stated that normal vigorous ciliary activity usually exists within a sinus, even in instances in which there is present an overwhelming chronic infection.

From the Department of Surgery, The Presbyterian Hospital of the City of Chicago, affiliated with the University of Illinois School of Medicine, Chicago.

METHODS

Eighteen mongrel dogs were anesthetized with intravenous nembutal by using 25 milligrams per kilogram of body weight. Under aseptic conditions, the trachea was exposed from upper sternum to cricoid cartilage. The cervical trachea was freed and transsected at each end, and a free length of trachea of 14 or more cartilaginous rings was obtained. This autogenous tracheal graft was turned end for end, and the ends of the reversed segment were anastomosed in an airtight manner to the trachea distally and the first tracheal ring proximally.

The animals were autopsied at periodic intervals, and microscopic sections made of the grafted trachea. A serial record of the degeneration and regrowth of the epithelium was provided.

In 3 instances, a single animal had daily bronchoscopic biopsies of the epithelial lining of the grafted segment, but the tissue obtained for study was less satisfactory than the postmortem material.

Three dogs were allowed to live more than 6 weeks. The trachea was then opened in each dog at 9, 10, and 16 weeks, respectively, and the direction of the beat of the cilia in the reversed segment of the trachea was noted. One of these animals had his trachea closed following this observation and is living with his reversed graft 9 months after operation.

RESULTS

Fate of the ciliated respiratory epithelium in the autologous tracheal graft. During the first 4 days following the graft, the ciliated columnar cells die and slough (Fig. 1). Only

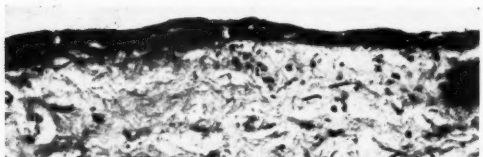


FIG. 1. The ciliated columnar epithelium has been replaced by low cuboidal cells. There is no evidence of the presence of living cells deep to the layer of cuboidal epithelium.

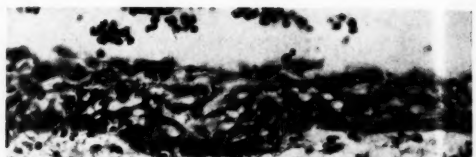


FIG. 3. The graft shows small blood vessels in submucosa with regeneration of the epithelium from the basal cuboidal cells. The regenerating epithelium resembles squamous metaplasia.

the basal layer of cuboidal cells line the grafted segment. There is an absence of granulation tissue in the submucosal areas, which show only the ghosts of disintegrating dead cells and areolar tissue.

By the eighth postoperative day (Fig. 2) it is noted that the cuboidal remnant of the lining still survives in a significant portion of the surface area of the graft.

By the eighteenth day (Fig. 3) granulation tissue is in evidence beneath the cuboidal layer of cells which are beginning to form a second layer.

At 23 days (Fig. 4) the graft has good vascularity and is lined with ciliated columnar type cells. This epithelial lining apparently regenerated from the basal layer of cuboidal cells.

Direction of ciliary motion in reversed tracheal graft. Under general anesthesia, the trachea was opened in the midline. A small drop of India ink was deposited on the mucous sheet which lines the tracheobronchial tree at a point near the cephalad end of the graft. Another drop was placed 3 centimeters below the grafted segment on the mucous lining of the normal trachea. The ink placed on the graft was propelled caudad, while the ink placed on the normal trachea moved cephalad. The two deposits of ink moved toward each other at approximately the same rate.

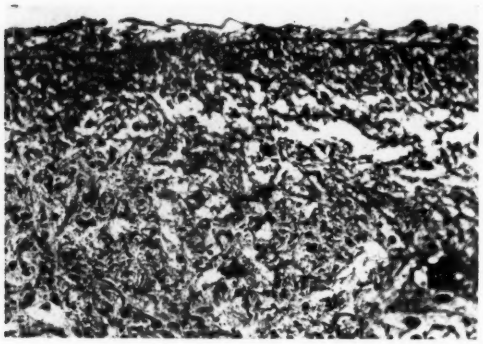


FIG. 2. Islands of flat to cuboidal cells still represent remnants of the tracheal epithelium. Pyknotic nuclei and cellular debris are present beneath the mucosa.

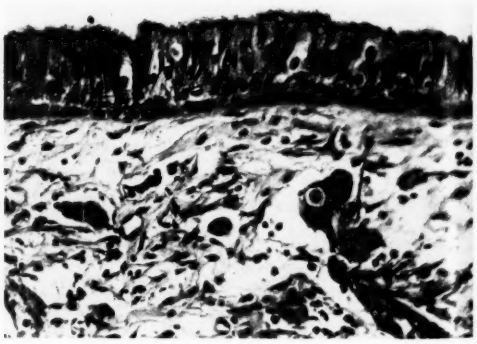


FIG. 4. Ciliated columnar epithelium now easily identified. The basal layer of cuboidal cells seems somewhat prominent.

DISCUSSION

These observations suggest that, in the dog, the destroyed respiratory epithelium lining the trachea requires 3 to 4 weeks to regenerate in the reversed autogenous graft. The ciliated columnar epithelium thus regenerated is apparently the progeny of basal cuboidal cells, islands of which survive the period of revascularization of the graft. The rate and manner of such regeneration are similar to that described in the paranasal sinuses.

The cilia of the regenerated epithelial lining of the trachea have been demonstrated to retain their original direction of beat with respect to the grafted segment housing them. Thus, in the reversed autogenous tracheal graft, the overlying mucous sheet is propelled caudad. This factor has been demonstrated to cause a "piling up" of mucous at the caudad anastomosis in dogs subjected to such reversal grafts. It is interesting to note that such animals suffer little inconvenience from such a ring of mucous in the midportion of their tracheas, although they are forced to cough it out occasionally. Their horizontal tracheas of relatively large caliber may account for their not having trouble with retained secretions. No doubt another significant factor in their survival is the fact that the cilia of the lower trachea and bronchi are presumably effective in keeping their lungs clear of mucous secretions.

SUMMARY AND CONCLUSIONS

1. Reversal of a 2 to 3 inch segment of the cervical trachea was performed in 18 dogs. These dogs were autopsied after various intervals to study the rate of regeneration of the respiratory epithelium lining.

2. The ciliated columnar cells disappear, leaving a layer of cuboidal cells. The basal layer of cuboidal cells apparently gives rise to normal appearing ciliated columnar epithelium in 3 to 4 weeks.

3. The direction of beat of the regenerated cilia is the same as the original cilia of the grafted segment. Therefore, the "mucous river" of a reversed segment of trachea flows caudad.

REFERENCES

1. GORHAM, C. B., and BACHER, J. A. Regeneration of human maxillary antral lining. Arch. Otolar., Chic., 1930, 11: 763.
2. KNOWLTON, C. D., and MCGREGOR, G. W. How and when the mucous membrane of the maxillary sinus regenerates; an experimental study in the dog. Arch. Otolar., 1928, 8: 67.
3. LATTA, J. S., and SCHALL, R. F. The histology of the paranasal sinuses under various conditions. Ann. Otol. Rhinol., 1934, 43: 945.
4. PROETZ, A. W. Studies of nasal cilia in the living mammal. Ann. Otol. Rhinol., 1933, 42: 778.
5. Idem. Essays on the Applied Physiology of the Nose. St. Louis: Annals Publishing Co., 1941.

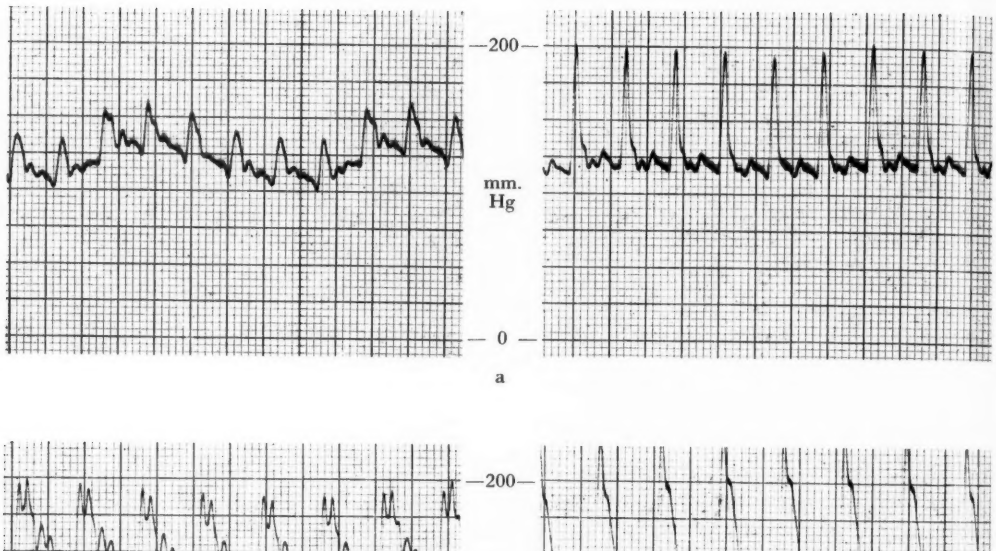


FIG. 1. Arterial pressure tracings. a, Normal control. b, Operative control; aorta divided at 2 levels and reanastomosed.

Hemodynamic Changes Resulting from Blood Vessel Grafts and Prostheses.—Worthington G. Schenk, Jr., James H. Cosgriff, Jr., and James G. Gray.

HEMODYNAMIC CHANGES RESULTING FROM BLOOD VESSEL GRAFTS AND PROSTHESES

WORTHINGTON G. SCHENK, JR., M.D., JAMES H. COSGRIFF, JR., M.D., and JAMES G. GRAY, M.D., Buffalo, New York

ARTERIAL RECONSTRUCTION BY use of arterial homografts or prosthetic material has been a very gratifying surgical advance as confirmed by a profusion of successful reports in the current surgical literature. A wide variety of methods for collection, sterilization, processing, and storage of homografts has been devised. More recently prosthetic materials—vinyon-N, orlon, nylon, and others—have been investigated as arterial replacements. Many reports are available confirming the fact that arterial homografts prepared and stored by a wide variety of methods result in an anatomically acceptable channel after implantation. More difficulties have been encountered in replacement of an arterial segment with a prosthetic material but a number of reports attest to the fact that an adequate anatomic channel can result from implantation of several of the currently available prosthetic materials into experimental animals and patients.

Little has been done to evaluate the hemodynamic changes, if any, which result from implantation of homografts and prostheses. We have addressed ourselves to this part of the problem, being particularly interested in attempting to determine whether any evidence could be obtained to indicate functional superiority of one type of homograft or prosthesis.

METHOD

Arterial pulse wave form tracings were made at various levels in the major arterial system of the dog using an intra-arterial catheter introduced through the femoral artery in conjunction with the Sanborn electromanometer. A series of control tracings was made to determine whether or not a consistent pressure or pulse wave gradient existed in the normal animal.

By using hypothermia animals were prepared in which thoracic aortic segments were replaced by (1) frozen homografts, some taken aseptically, others sterilized with beta propriolactone, and all stored at −70 degrees C., and (2) prostheses constructed of vinyon-N, orlon, and crimped nylon.

Follow-up pressure studies were carried out at intervals along with aortography to assure that an anatomically adequate channel existed. No animal was included in the study unless the reconstruction was satisfactory on aortography.

RESULTS

Controls. Eleven normal dogs were studied to determine whether a consistent pulse pressure gradient existed between the aortic arch and the femoral artery. We had expected a gradient to exist but were somewhat surprised by the direction and magnitude of this gradient. Reference to the classical physiologic teaching of Best and Taylor indicates that we should expect a progressive narrowing of pulse pressure from the aortic arch toward the periphery. Our observations indicate that precisely the reverse occurs. There is a consistent, rather marked widening of pulse pressure from the aortic arch to the femoral artery. In the 11 dogs studied there was an average increase of 76 per cent in the pulse pressure from the aortic arch to the femoral artery with a range of 43 to 110 per cent increase. As seen in the tracing

From the Department of Surgery, University of Buffalo Medical School and Edward J. Meyer Memorial Hospital, Buffalo.

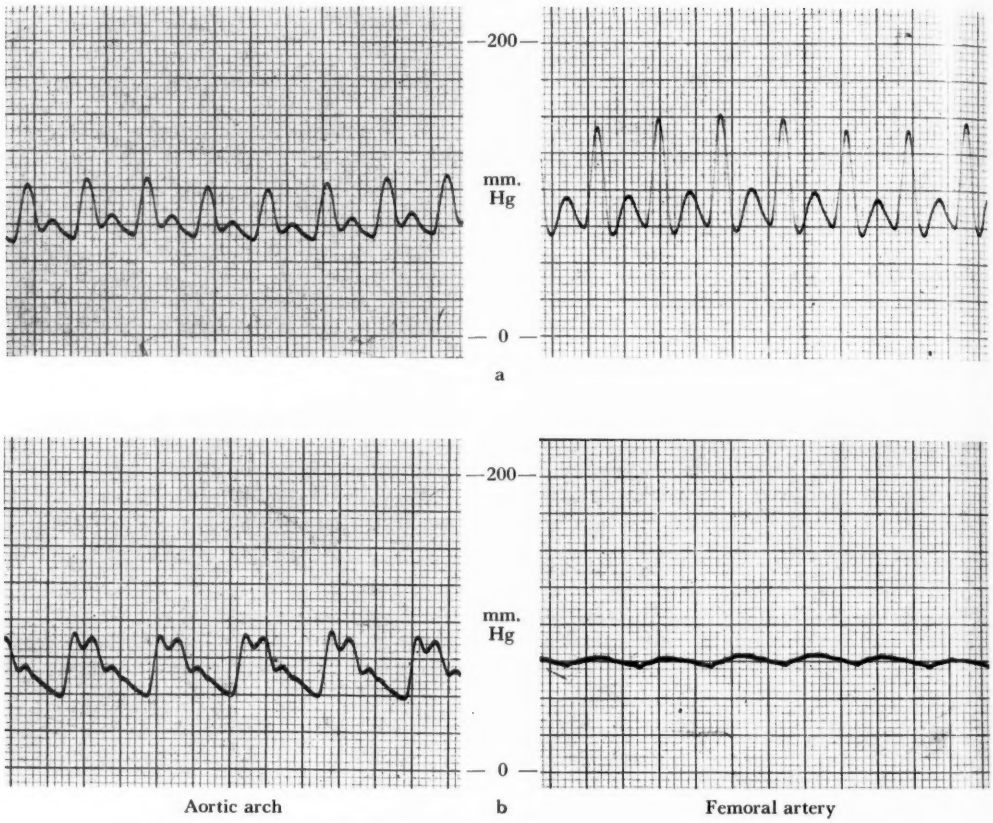


FIG. 2. Arterial pressure tracings. a, Preoperative study. b, Study with glass cannula replacing thoracic aortic segment.

(Fig. 1a) from 1 such control, the increased pulse pressure results both from a decrease in diastolic pressure and an actual increase in systolic pressure. The diastolic decreases somewhat more than the systolic increases so that mean pressure falls as might be anticipated. The most significant observation would seem to be that the peripheral systolic pressure uniformly exceeded the central systolic pressure generated by the same heartbeat. This observation was reported by Hamilton (2, 3) in 1936 and has recently been confirmed by Kroeker and Wood.

As an operative control the aorta was divided and reanastomosed in 2 dogs at the same levels at which suture lines were made in the replacement experiments. Figure 1b shows the tracings from 1 experiment made 90 days after division and reanastomosis. The pulse pressure increase is 77 per cent from the aortic arch to the femoral artery—almost identical to the control groups, and with similar wave form. The second identical control studied at 90 days showed a 57 per cent pulse pressure increase, also well within the range of the normal controls.

Experimental group. As an initial experiment to determine whether the relative elasticity or rigidity of a vascular replacement might be expected to have any influence on pulse wave transmission, a 4 centimeter long glass cannula was used to replace a resected thoracic aortic segment. Immediate recordings made with this completely rigid conduit

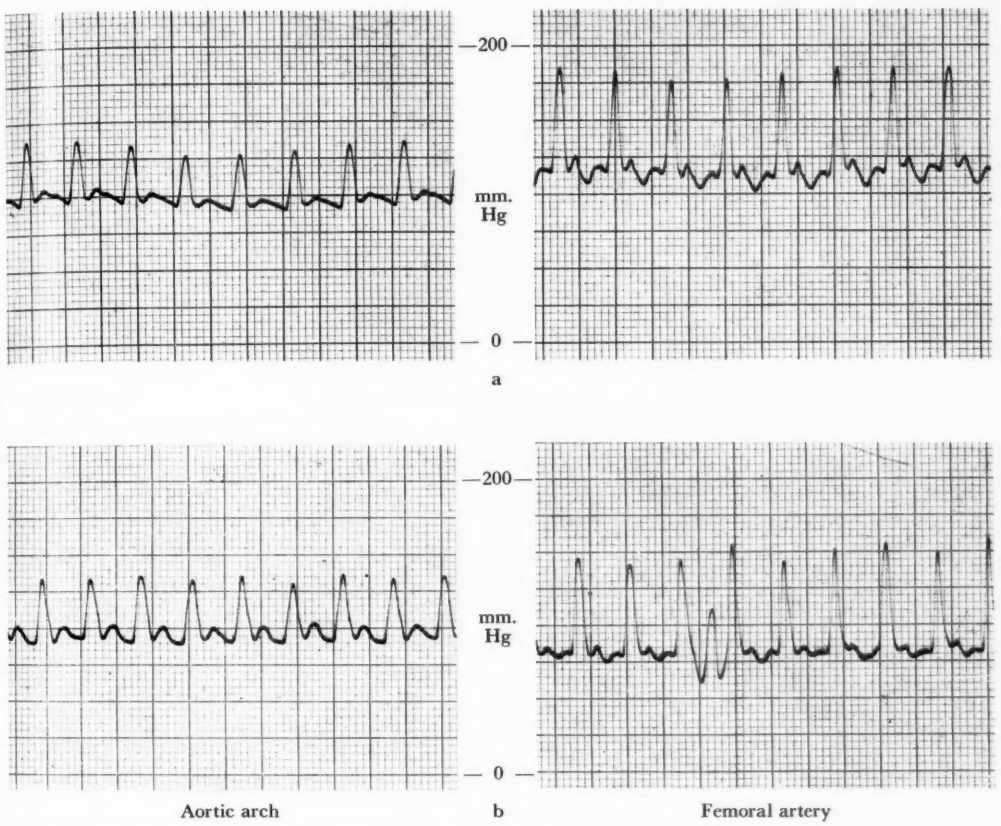


FIG. 3. Arterial pressure tracings. a, Preoperative study. b, Immediately following thoracic aortic homograft.

in place are shown in Figures 2a and 2b. In Figure 2a the preoperative study is shown with a pulse pressure increase of 100 per cent from aortic arch to femoral artery. In Figure 2b the recordings are seen with the glass cannula in place, showing a decrease in the pulse pressure of 700 per cent from the aortic arch to the femoral artery.

Since it was thus apparent that insertion of a completely rigid conduit into the proximal arterial system interfered markedly with the pulse wave transmission, it was decided to determine the degree to which the currently used grafts and prostheses interfere with pulse wave transmission.

Homografts. Frozen homografts, 3 to 6 centimeters in length, were implanted end-to-end into the thoracic aorta of 3 dogs under hypothermia after a 50 per cent shorter segment had been excised. A similar homograft was implanted into a fourth dog using a glass cannula as an internal shunt to permit the operation without hypothermia so that an immediate postoperative pressure study could be made without the cardiovascular effects of hypothermia interfering. Pressure studies were carried out on the latter dog immediately postoperatively and on the other 3 animals after 90 days.

Figure 3a shows the preoperative study and Figure 3b the immediate postoperative study. It will be noted that there has been a slight diminution in the distal pulse pressure gradient in the postoperative study, but that

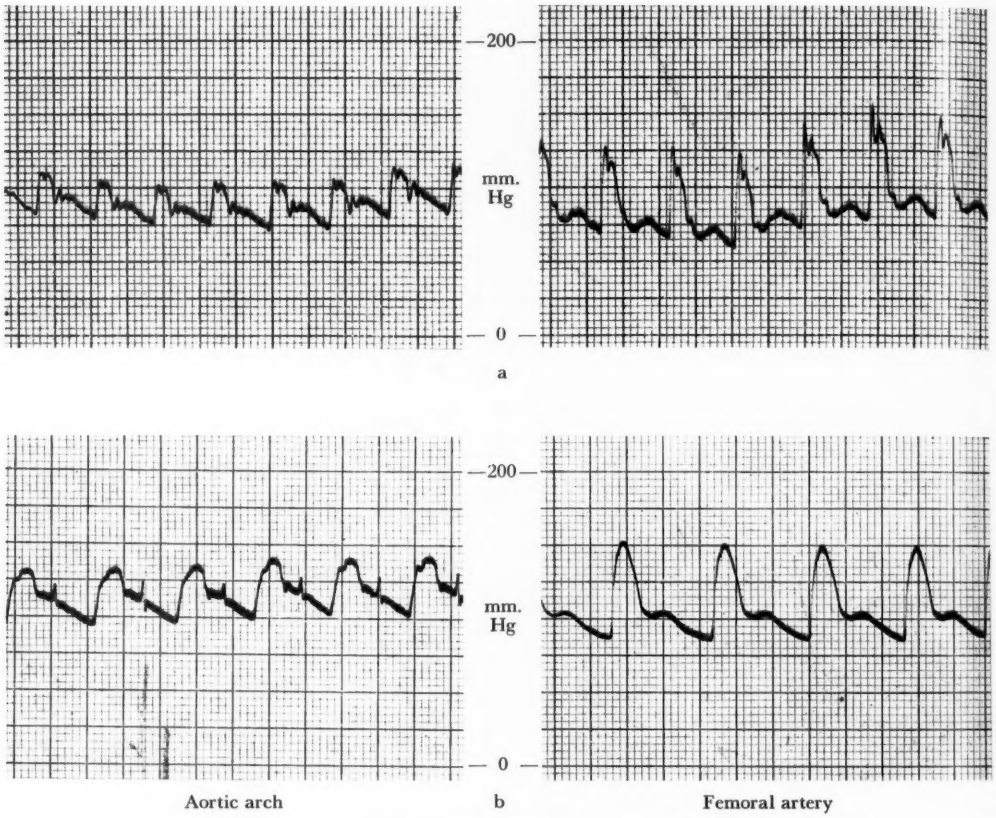


FIG. 4. Arterial pressure tracings. a, Preoperative study. b, Ninety days after thoracic aortic homograft.

it is still well within the control range (86 per cent increase).

Figure 4a shows the preoperative study, and Figure 4b the postoperative study of an animal 90 days after thoracic aortic homograft. The 3 month tracing shows a pulse pressure increase of 85 per cent, well within normal range. The other 2 animals studied at 90 days showed 80 and 77 per cent increases, also well within normal range.

Prostheses. Cloth prostheses in lengths similar to the homografts described were implanted into the thoracic aorta of 5 dogs by identical technique.

Vinyon-N was implanted in 2 dogs: the first without hypothermia, and pressure studies were carried out immediately postoperatively; the second with hypothermia and studies were made at 90 days. Figure 5a shows the immediate postoperative study. There was a 25 per cent decrease in pulse pressure from aortic arch to the femoral artery. The vinyon-N prosthesis pressure study at 90 days is shown in Figure 5b. The pulse pressure dropped 15 per cent from the aortic arch to the femoral artery.

An orlon thoracic prosthesis showed a pulse pressure decrease of 8 per cent when studied at 6 weeks, and a nylon prosthesis showed no change in femoral as compared with aortic arch pressure at 6 weeks.

Finally, an attempt was made to evaluate the effect on pulse wave transmission of a very long by-pass prosthesis. Under hypo-

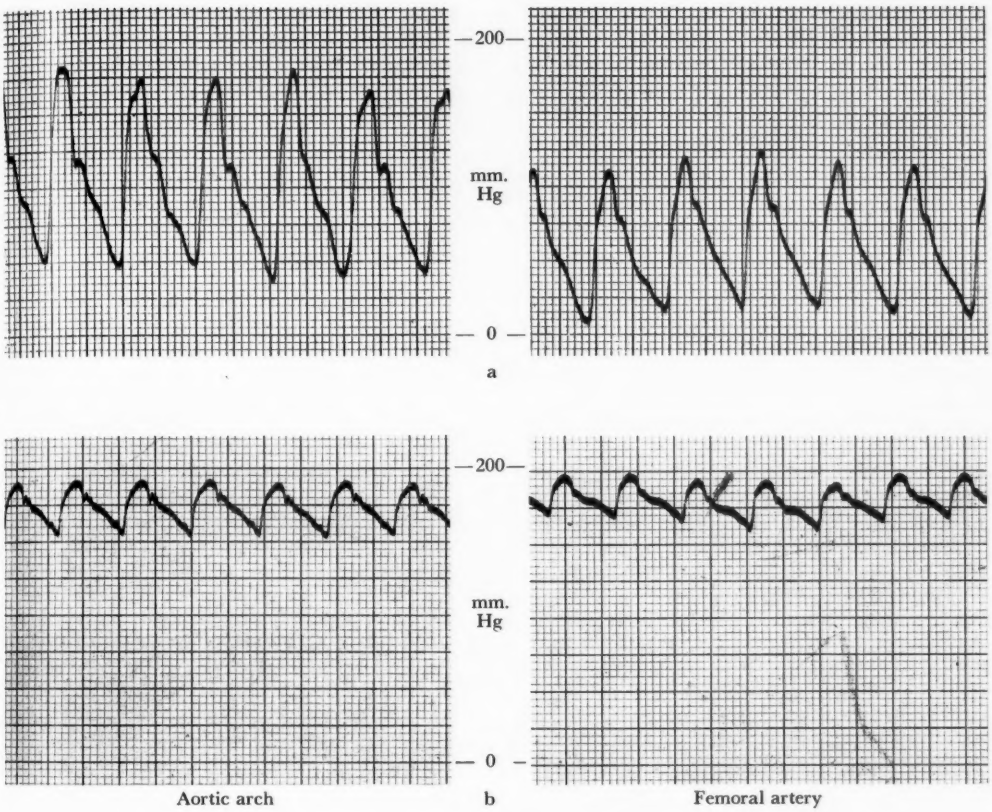


FIG. 5. Arterial pressure tracings—vinyon "N" thoracic aortic prosthesis. a, Immediately postoperative. b, Ninety days after operation.

thermia a crimped nylon prosthesis was anastomosed to the proximal segment of the high thoracic aorta, end-to-end; and to the abdominal aorta just proximal to the trifurcation, end-to-side, as illustrated in Figure 6. The distal thoracic aorta was ligated at the level of transection. This by-pass was 9 inches long. The preoperative and immediately postoperative studies are shown in Figures 7a and 7b, respectively, where the tracing on the left was recorded at point *A* and that on the right at point *B*. The marked reduction in distal pulse pressure (60 per cent) resulting from the by-pass is apparent.

The findings from this last described preparation are in rather sharp contrast to the final experimental preparation which is identical to the last described in Figure 6 except that the long by-pass was made by utilizing a frozen aortic homograft rather than a crimped nylon prosthesis. Figure 8a shows the preoperative pressure studies at points *A* on the left and *B* on the right. This is comparable to control tracings. The immediately postoperative pressure study is shown in Figure 8b. The pulse pressure increase was somewhat less in the postoperative study than preoperatively, but there was an approximate 40 per cent increase in pulse pressure from the aortic arch to the femoral artery in the long homograft by-pass, while there was a 60 per cent decrease in pulse pressure over the same vascular interval after crimped nylon by-pass.

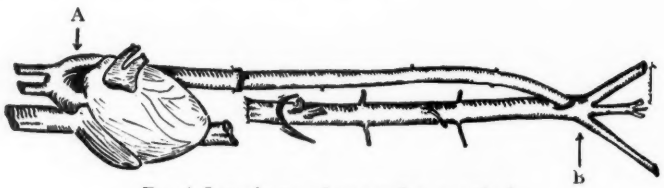


FIG. 6. Long by-pass homograft or prosthesis.

DISCUSSION

It is apparent from the material presented that under the experimental circumstances described cloth arterial prostheses interfere rather markedly with pulse pressure while homografts interfere very little. It becomes of importance to know, then, if it makes any difference whether the arterial pressure be pulsatile or not so long as the mean pressure is maintained. Evidence has been supplied by Wesolowski and Welch which bears rather directly on this point. They found that it was impossible to maintain normal arterial blood pressure in the experimental animal for longer than 1 hour by using a nonpulsatile blood pump, even though the dogs were

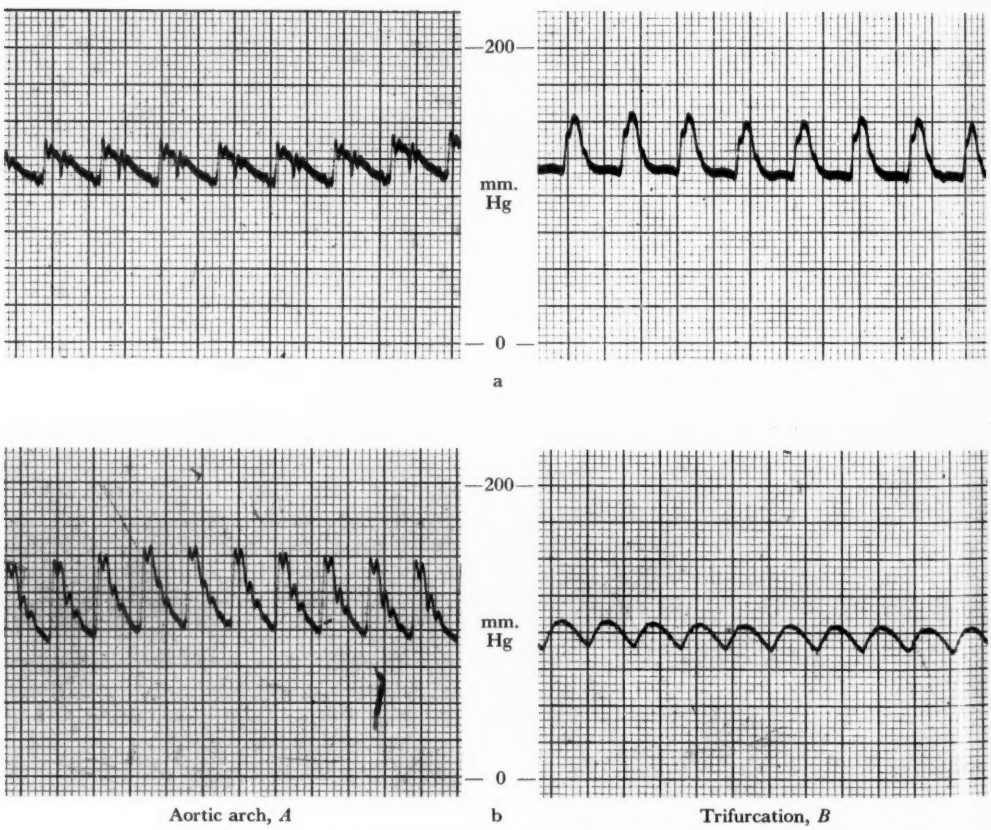


FIG. 7. Arterial pressure tracings. a, Preoperative study. b, Immediately after implantation of long by-pass prosthesis.

overtransfused to the point where fatal pulmonary edema ensued after resumption of normal cardiac output. They concluded: "An extracorporeal heart pump that delivers a pulsatile type of flow seems preferable to a pump mechanism which delivers a nonpulsatile type of flow. It appears that the pulse has a definite physiologic role in the maintenance of peripheral vasomotor tone, and therefore, of arterial blood pressure."

It would seem that a pulsatile flow is desirable and that on the basis of these relatively short term observations, arterial homografts are preferable to cloth prostheses simply because they do not interfere with pulse pressure. It is quite possible, of course, that long term degenerative changes in homografts will render them completely rigid and, therefore, functionally equivalent to prostheses, but up to 1 year postimplantation homografts retain this functional superiority.

It is not an easy matter to explain the progressive increase in pulse pressure which occurs toward the periphery in the arterial system. Attempts to apply the known laws of fluid dynamics to the arterial system seem to increase the confusion rather than to diminish it since those laws apply only to rigid systems. Not only is the arterial tree not a rigid system but its caliber varies markedly from point to point, branching occurs at frequent intervals, the system has

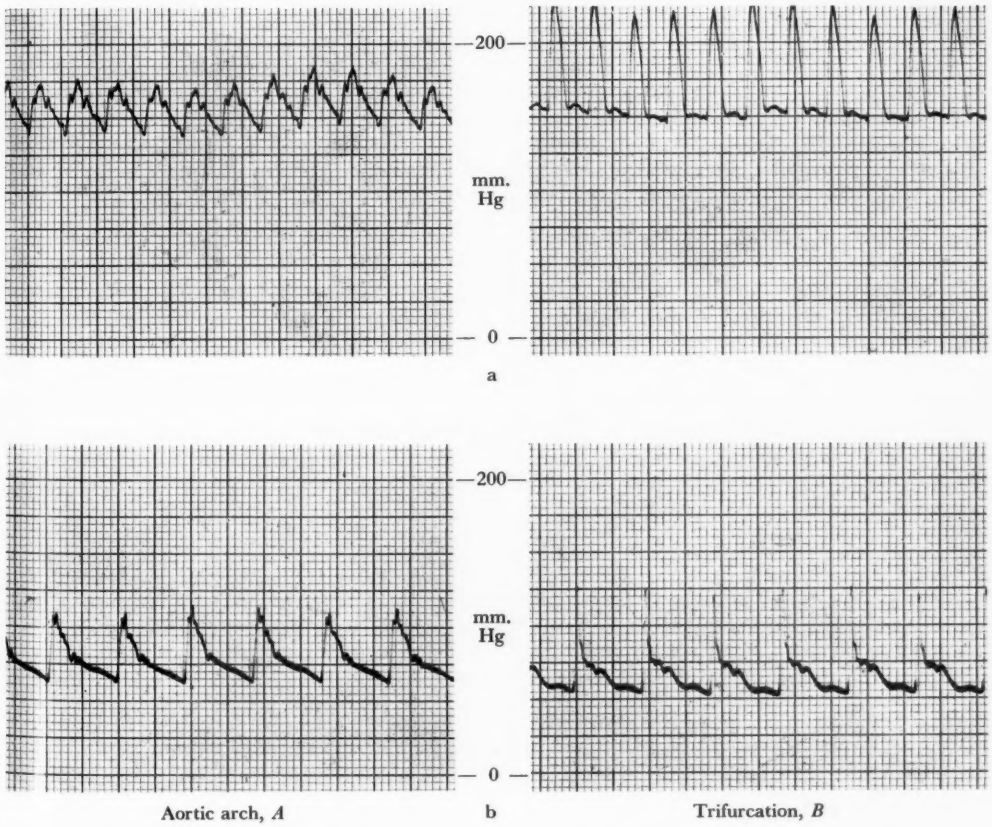


FIG. 8. Arterial pressure tracings. a, Preoperative study. b, Immediately after implantation of long by-pass homograft.

marked distensibility with passive elastic recoil, and finally, the system has the ability to contract actively and segmentally. Postulation of an "arterial systole" is one possible mechanism to explain the changes which were observed.

SUMMARY AND CONCLUSIONS

1. There is a marked widening of pulse pressure in the femoral artery as compared with the aortic arch in the dog. On the average the femoral pulse pressure was found to be 76 per cent greater than the aortic arch pulse pressure.

2. The peripheral systolic pressure uniformly exceeded the central systolic pressure generated by the same heartbeat.

3. Simple division and reanastomosis of the thoracic aorta at 1 or 2 levels did not interfere with pulse wave transmission.

4. Insertion of a completely rigid conduit into the proximal arterial system interfered markedly with the pulse wave transmission.

5. Little or no interference with pulse wave transmission was produced by the implantation of frozen thoracic aortic homografts.

6. Marked interference with pulse wave transmission resulted from implantation of cloth prostheses into the thoracic aorta.

7. Since a pulsatile flow in the arterial tree has previously been shown to be superior to a nonpulsatile flow, arterial homografts would seem to have a functional superiority over any of the currently available prosthetic materials, at least up to 1 year after implantation.

REFERENCES

1. Best, C. H., and Taylor, N. B. The Physiological Basis of Medical Practice. P. 200. Baltimore, Md.: The Williams & Wilkins Co., 1943.
2. Hamilton, W. F. The patterns of the arterial pressure pulse. Am. J. Physiol., 1944, 141: 235.
3. Hamilton, W. F., Woodbury, R. A., and Harper, H. T., Jr. Physiological relationships between intrathoracic, intraspinal, and arterial pressures. J. Am. M. Ass., 1936, 107: 853.
4. Kroeker, E. J., and Wood, E. H. Comparison of simultaneously recorded central and peripheral arterial pressure pulses during rest, exercise, and tilted position in man. Circulation Res., 1955, 3: 623.
5. Wesolowski, S. A., and Welch, C. S. Experimental maintenance of the circulation by mechanical pumps. Surgery, 1952, 31: 769.

A STUDY OF 531 CASES OF ENDOMETRIAL CARCINOMA

JOHN H. RANDALL, M.D., F.A.C.S., and WILLIAM B. GODDARD, M.D., Iowa City, Iowa

DURING THE PERIOD from January 1926 to January 1951, 531 patients with endometrial carcinoma were admitted to the University of Iowa Hospitals. During this same period, 1,558 patients with cervical carcinoma were treated, making the ratio of cervical to endometrial cancer approximately 3 to 1. It is the purpose of this article to present a statistical analysis and summary of the cases of endometrial carcinoma.

The majority of the patients were indigent and lived within the state of Iowa. The entire group of patients who survived were followed for 5 or more years after completion of therapy. All deaths have been considered to be due to endometrial cancer unless by postmortem examination it could be proved that there was no residual cancer. No correction has been made for natural attrition.

Endometrial cancer was essentially a postmenopausal disease. In the series only 20 per cent of the patients were still menstruating. Endometrial cancer was uncommon in patients under the age of 40 (2.62 per cent, Table I). The greatest incidence was in the age group of from 50 to 59 years. The average age at diagnosis was 59.2 years. The youngest patient was 24 years old and the oldest was 86. In the past 6 years of the survey, the number of patients 70 years of age or over has slightly more than doubled the average number noted for the preceding years.

This increment has been due to the increased longevity of women which has resulted from the marked advances in medicine made in recent years.

One hundred thirty-eight patients (25.98 per cent) had never been pregnant (Table II). Thus, it appears that childbearing does not favor but rather decreases the chances of developing endometrial cancer. The average parity demonstrated for the entire series was 2.6.

There was an increased tendency for patients with endometrial cancer to be obese. In the series, 308 patients (58 per cent) weighed 170 pounds or over. Bastiaanse, Scheffey, and Waterman, Raphael, and Moskosky have also observed a relationship between obesity and the incidence of the disease. Extreme degrees of obesity have made inoperable many cases in the series which were operable as far as the extent of the disease was concerned.

Fifty-eight per cent of the patients menstruated beyond the age of 50 and can be considered to have had a late menopause. Peightal and Crawford, Way, and Palmer, Reinhard, Sadugor, and Goltz have emphasized a relationship between the incidence of endometrial carcinoma and delayed menopause. Twenty-nine patients had an artificial menopause, 13 with x-rays, 9 with radium, and 7 by previous bilateral oophorectomy. It has been claimed by Kimbrough that a radiotherapeutic menopause favors the development of endometrial cancer while other authors have believed that surgical castration makes it less likely.

The most common initial symptom was vaginal bleeding (94.91 per cent, Table III). Any vaginal bleeding which occurs after the menopause, or between menstrual periods in women 40 or more years of age, is suggestive of endometrial cancer and should be investigated by curettage if carcinoma cannot be demonstrated in the cervix or lower genital tract. No benign lesion should ever be offered as an explanation for metrorrhagic bleeding until malignant causes have been thoroughly investigated. Leucorrhea was the initial symptom in 18 patients (3.38 per cent). Other symptoms were seen

From the Department of Obstetrics and Gynecology, State University of Iowa Hospitals, Iowa City, Iowa.

TABLE I.—AGE IN RELATION TO ENDOMETRIAL CARCINOMA

	Cases		5 yr. survivals	
Age, yrs.	*No.*	*Per cent*	*No.*	*Per cent*
20–29	2	.37	2	100.00
30–39	12	2.25	10	83.33
40–49	55	10.35	36	65.45
50–59	208	39.17	124	59.61
60–69	174	32.76	83	47.70
70–79	76	14.31	30	39.47
80–89	4	.75	0	0.00
Total	531	100.00	285	53.67

only in advanced cancer and were of no practical significance for making an early diagnosis. In fact, it must be emphasized that if endometrial carcinoma is to be suspected from the clinical picture, irregular bleeding is the chief symptom to which the physician must give particular attention.

All patients have been divided into 4 groups according to the stage of the disease. The staging was usually done at the initial examination but in some cases a modification was necessary when the exact extent of the neoplastic process was more definitely determined at the time of operation. Stage 1 included those cancers involving only the body of the uterus. In stage 2, the malignant process had extended down through the internal os to involve the cervical canal but not the portio of the cervix. In stage 3, the cancer was not confined to the uterus but was still localized to the genital tract. Most of the patients in this group had either vaginal metastases or some spread into the broad ligaments. Stage 4 embraced those cancers which spread beyond the genital tract, involving peritoneal surfaces, regional or distant nodes, or contiguous or distant organs. Most of the patients had stage 1 carcinoma (61.95 per cent, Table IV). Stage 1 and 2 carcinomas were considered to be technically operable. The patients who had received initial treatment in other institutions and who were sent to the University Hospitals with a recurrence could not be definitely grouped as to the stage of disease. Although there have been many educational campaigns to spread knowledge of the early symptoms of uterine cancer among various lay groups, during the past 6 years, there has been an increase in the number of inoperable cases (stages 3 and 4) from 14.2 per cent in previous years to 21.4 per cent.

TABLE II.—PARITY IN RELATION TO SURVIVALS

	Cases		5 yr. survivals	
Parity	*No.*	*Per cent*	*No.*	*Per cent*
None	138	25.98	72	52.17
One	71	13.37	28	39.43
Two	89	16.76	50	56.17
Three	69	12.99	42	60.86
Four	47	8.85	27	57.44
Five	37	6.96	24	64.86
Six	28	5.27	18	64.28
Seven	14	2.63	7	50.00
Eight or over	20	3.76	7	35.00
Unknown	18	3.39	10	55.55
Total	531	100.00	285	53.67

In 501 patients it was possible to divide the endometrial carcinomas into 4 histologic groups according to the degree of cell differentiation (Table V). The cells of grade 1 carcinomas were the most markedly differentiated while those of grade 4 were the least. The method of grading used has been described in detail by Randall and Mirick in a previous publication. Almost one-half of the cases were of grades 1 and 2 (48.7 per cent), thus explaining the low degree of malignancy of many endometrial carcinomas. One patient had epidermoid carcinoma, 6 had a combination of carcinoma and sarcoma, and 23 had tumors which could not be classified because primary treatment had been received in other hospitals. Thirty-three (6.6 per cent) mature adenocarcinomas (grade 1 or 2) showed a definite tendency to undergo squamous metaplasia and were called adenoacanthomas.

At the University Hospitals, endometrial carcinomas have always been treated surgically if it was at all feasible (60 per cent). The operation performed usually has been an abdominal total hysterectomy with complete removal of the adnexa on each side. Prior to 1935 hysterectomy alone, or in combination with deep x-ray therapy, was the preferred treatment. Since 1935 it has been the policy to precede hysterectomy by an application of intracavitary radium. At first a tandem applicator using two 25 milligram tubes of radium was used. Since 1942, the procedure has been to pack the uterine cav-

ity with multiple foci of radium, each containing 10 milligrams of radium and filtered with 1 millimeter of platinum. The radium was applied immediately following a diagnostic curettage and was allowed to remain for 3 days if a 24 hour report from the Department of Pathology confirmed the diagnosis of endometrial carcinoma. Intrauterine radium was used irrespective of the grade of carcinoma. In 6 to 8 weeks, the patient was readmitted to the hospital for a hysterectomy performed according to the following technique: The uterine cavity was packed with gauze and the external os of the cervix closed with sutures. Immediately after opening the abdomen, the distal end of each tube was ligated to prevent any spillage from squeezing the uterine body. The uterus along with the entire adnexa on each side was removed with as little trauma as possible. The only patients who did not receive intracavitary radium prior to hysterectomy were those in whom the uterus was perforated at the time of diagnostic curettage or irregularly enlarged with multiple fibroids.

Radium has been used alone in stage 1 and stage 2 cases, or in combination with deep x-ray therapy in some of the stage 2 cases considered to be inoperable because of some associated disease or obesity, or when operation was refused.

Patients with stage 3 carcinomas usually have been treated with intrauterine radium combined with x-ray therapy to the lower abdomen and pelvis. Some of this group in whom extension of the disease beyond the uterus seemed doubtful have had a hysterectomy after preliminary irradiation with intrauterine radium and deep x-ray therapy. In others vaginal metastatic nodules have been treated with interstitial radium and the primary uterine tumor with intracavitary radium combined with deep x-ray therapy. Patients with stage 4 carcinomas have usually been treated with intrauterine radium combined with deep x-ray therapy or x-irradiation alone.

Altogether, there have been 531 patients with endometrial carcinoma examined at the

TABLE III.—INITIAL SYMPTOM OF ENDOMETRIAL CARCINOMA

	Cases		5 yr. survivals	
Symptom	*No.*	*Per cent*	*No.*	*Per cent*
Bleeding	504	94.91	275	54.56
Leucorrhea	18	3.38	7	38.88
Unknown	9	1.69	3	33.33
Total	531	100.00	285	53.67

University Hospitals, and of this number 516 were treated, with an apparent 5 year recovery rate of 53.6 per cent. These results are similar to those published by Heyman in the *Tenth Annual Report on the Results of Treatment in Carcinoma of the Uterus.* In 1955, he was able to collect 8,366 cases of endometrial carcinoma from 84 collaborators, with a 5 year recovery rate of 52.4 per cent.

One hundred ninety-four patients were treated first with intracavitary radium followed by a hysterectomy performed 6 to 8 weeks later. In this group there were 147 5 year survivals or 75.77 per cent (Table VI). It is interesting to compare the results of this group with those in a comparable series of 99 patients who were treated by hysterectomy alone, or hysterectomy combined with x-ray therapy. In the group treated by hysterectomy without intracavitary radium there were 58 five year survivals (58.5 per cent). Heyman reported a collective series of 2,405 patients primarily treated by hysterectomy with a relative 5 year recovery rate of 57 per cent. Thus, intracavitary radium followed by hysterectomy seems to yield better results than hysterectomy alone or in combination with x-ray therapy.

Seventy-one patients were treated only with intracavitary radium. Of these, there were 35 five year survivals or 49.29 per cent. Seventy-six patients were treated with radium and x-ray with 18 five year survivals. Most of the patients of this group had ad-

TABLE IV.—STAGE OF DISEASE IN RELATION TO SURVIVALS

	Cases		5 yr. survivals	
Stage	*No.*	*Per cent*	*No.*	*Per cent*
1	329	61.95	232	70.51
2	45	8.47	20	44.44
3	40	7.53	3	7.50
4	50	9.41	1	2.00
Unknown	67	12.61	29	43.28
Total	531	100.00	285	53.67

TABLE V.—GRADE OF ADENOCARCINOMA* IN RELATION TO SURVIVALS

	Cases		5 yr. survivals	
Histologic grade	*No.*	*Per cent*	*No.*	*Per cent*
1	47	9.38	42	89.36
2	197	39.32	119	60.40
3	194	38.72	90	46.39
4	63	12.57	19	30.16
Total	501	100.00	270	53.89

*Epidermoid carcinoma 1 case, carcinosarcoma 6 cases, and unclassified carcinomas 23 cases.

vanced lesions of stages 3 or 4. Preoperative or postoperative x-irradiation has been less efficacious than intracavitary radium prior to hysterectomy. Of 59 patients treated with a combination of x-ray therapy and hysterectomy, there were 34 five year survivals (57.62 per cent). Because of a protective layer of myometrium, intrauterine radium can be safely given in a dosage sufficiently high to be effective in sterilizing many uteri of cancer. Many patients who have endometrial cancer are over the age of 60 years and cannot tolerate deep x-ray therapy in the dosage required to destroy cancer within the uterine cavity or that which has spread beyond the confines of the uterus.

Multiple foci of radium have proved more effective in sterilizing the uterine cavity of cancer than 2 or more foci in a tandem applicator. Seventy-six patients were treated with a tandem applicator, and from this group, 25 uteri (33 per cent) showed no residual carcinoma when examined by the pathologist. There were 132 patients who had multiple foci of intracavitary radium prior to hysterectomy and of these, 82 patients had a complete sterilization (62.1 per cent). Residual cancer was determined by a thorough examination of several blocks of tissue taken from areas in which there seemed to be gross remnants of cancerous tissue. It seemed that cancer which had invaded the myometrium was more difficult to destroy. The salvage of patients has been roughly proportional to the number of complete sterilizations. The 5 year survivals of those who had residual carcinoma after multiple foci of radium constituted 61.3 per cent as contrasted with 76.3 per cent, the 5 year survival rate of those who had a complete sterilization. It is interesting to note that patients with residual carcinoma after a tolerance dosage of intrauterine radium were never cured by subsequent applications of radium. Therefore, it seems that those who do not get a complete sterilization after the initial treatment with intrauterine radium can be salvaged only by a complete hysterectomy. Since the use of preoperative intracavitary radium, recurrence in the vaginal apex has been eliminated. Recurrences are seen, but occur higher up in the pelvis or in regional nodes or distant organs.

TABLE VI.—TYPE OF THERAPY IN RELATION TO SURVIVALS

	Cases		5 yr. survivals	
Therapy	*No.*	*Per cent*	*No.*	*Per cent*
Radium and hysterectomy	194	36.53	147	75.77
Radium and x-ray	76	14.31	18	23.68
Radium alone	71	13.37	35	49.29
Hysterectomy and x-ray	59	11.11	34	57.62
Hysterectomy alone	40	7.53	24	60.00
Radium, x-ray, and hysterectomy	24	4.52	11	45.83
X-ray alone	19	3.57	1	5.26
No treatment	15	2.82	0	0.00
Miscellaneous	33	6.21	15	48.38
Total cases: seen	531	100.00	285	53.67
Total cases: treated	516	97.17	285	55.23

An examination of Table IV definitely demonstrates that the stage of the carcinoma when treatment is undertaken is an important factor in prognosis. Of 374 patients who had technically operable carcinomas (stages 1 and 2), there were 252 five year survivals (67.4 per cent). Ninety patients had inoperable cancers (stages 3 and 4), and of this group there were 4 five year survivals (4.4 per cent). If only those patients with carcinomas limited to the body of the uterus (stage 1) were considered, the 5 year salvage would be 70.5 per cent. To improve end results, it is necessary to obtain more patients with early lesions, for advanced cases, regardless of the type of treatment, have a poor prognosis.

From Table V it can be seen that the histologic grade of an endometrial carcinoma is also important in prognosis. The salvage is usually proportional to the degree of cell differentiation. The well differentiated car-

cinomas grow slowly and remain localized to the endometrial cavity for a relatively long period of time, while the more anaplastic cancers spread rather quickly into lymph channels and veins to metastasize to regional nodes and distant organs. Regardless of the histologic grade, all patients with operable carcinoma have in recent years received intracavitary radium prior to hysterectomy. The dosage of radium which can be safely applied is just as effective in producing a sterilization of the uterine cavity in mature as in immature cancers. Thirty-three mature adenocarcinomas showed definite squamous metaplasia (adenoacanthoma) and in this group of patients there were 20 five year survivals (60.6 per cent).

The younger patients had a better prognosis than those in the older age groups (Table I). The probable explanation for this is the greater natural attrition in the older patients. Also, the number of patients under 40 years of age was too small to be statistically significant, so that definite conclusions cannot be drawn. Parity had no relation to end results (Table II).

The most common pelvic disease (Table VII) associated with endometrial carcinoma was uterine fibroids, 22.78 per cent. According to Novak, this is about the usual incidence of fibroids in women over the age of 30 years, and it is assumed that their presence had no effect upon the development of cancer. In some instances, they do produce an irregularity and enlargement of the uterine cavity, making curettage ineffective in the diagnosis of cancer and necessitating a modification of the method of therapy. Endocervical polyps were present in 7.5 per cent of the patients, and their importance lies in the fact that they sometimes lead to an erroneous explanation of slight irregular vaginal bleeding, when the real cause is an endometrial cancer higher up in the uterine cavity. There were 5 feminizing ovarian tumors (.9 per cent), and it is doubtful if they had any etiologic significance as far as the associated endometrial carcinoma was concerned.

TABLE VII.—ASSOCIATED PELVIC DISEASES

Disease	*No. of cases*	*Per cent*
None	184	34.65
Fibroids	121	22.78
Cervical polyps	40	7.53
Pelvic inflammatory disease	37	6.96
Ovarian benign tumors	10	1.88
Malignant tumors	7	1.31
Feminizing tumors	5	.94
Endometriosis	3	.56
Other	38	7.15
Unknown	105	19.77

The most common generalized disease associated with endometrial carcinoma was cardiovascular disease (43.69 per cent) (Table VIII). Most of these patients had simple hypertension which had little effect upon the end results of treatment. However, when the hypertension was associated with cardiac or renal complications, the longevity of patients was materially shortened and the immediate risks of surgery were enhanced. Thirty-seven patients had diabetes (6.96 per cent). Any etiologic relationship between diabetes and endometrial cancer is questionable, but its presence in a patient certainly reduces the 5 year survival rate which in this series was 37.8 per cent.

There has been a definite increase in the number of patients with endometrial carcinoma treated at the University Hospitals (Table IX). Since the year 1935, when intracavitary radium prior to hysterectomy became the preferred method of therapy, there has been an improvement in end results except for the period from 1945 to 1950.

TABLE VIII.—ASSOCIATED DISEASE IN RELATION TO SURVIVALS

	Cases		*5 yr. survivals*	
Disease	*No.*	*Per cent*	*No.*	*Per cent*
None	227	42.74	127	55.94
Vascular disease	232	43.69	127	54.74
Diabetes	37	6.96	14	37.83
Miscellaneous	35	6.59	17	48.57
Total	531	100.00	285	53.67

TABLE IX.—SURVIVAL RATE BY 5 YEAR PERIODS

	Cases		*5 yr. survivals*	
Period, yrs.	*No.*	*Per cent*	*No.*	*Per cent*
1926–1929	28	5.27	13	46.4
1930–1934	71	13.37	31	43.7
1935–1939	105	19.77	59	56.2
1940–1944	126	23.72	77	61.1
1945–1950	201	37.85	105	52.2
Total	531	100.00	285	53.67

During this period there was a decided increase in the number of older patients and in the number of patients with inoperable cancers. Both of these factors would tend to decrease the favorable results of therapy.

There were 12 deaths in the entire series of patients with endometrial carcinoma (2.2 per cent) and all occurred within a month after the initial treatment. One patient died from peritonitis following the insertion of radium, and another, 79 years of age, with severe cardiovascular disease, died following a diagnostic curettage. Ten patients who underwent hysterectomies died prior to 1946. Of these, 4 died from severe cardiovascular disease, 5 from peritonitis following hysterectomy, and 1 as the result of aspiration during anesthesia for a secondary closure performed because of an evisceration. Altogether 307 hysterectomies have been performed for endometrial carcinoma with 10 deaths (3.2 per cent). After the year 1946, there were no deaths in the series from any cause as the result of therapy.

SUMMARY AND CONCLUSIONS

1. From January 1926 to January 1951, 531 patients with endometrial carcinoma were admitted to the University of Iowa Hospitals for treatment. Of this number, 516 were treated, with a 5 year survival of 55.2 per cent.

2. Endometrial carcinoma was essentially a postmenopausal disease (80 per cent), was uncommon before the age of 40 (2.25 per cent), and occurred most frequently in the 50 to 59 year age group (39.17 per cent).

3. It was seen less commonly in childbearing women and was favored by obesity and late menopause.

4. Most of the cancers (374 or 70.4 per cent) were classified as stage 1 or 2 and were technically operable.

5. The carcinomas could be divided into 4 histologic grades, with approximately half being mature (grades 1 and 2) and the remainder, immature (grades 3 and 4).

6. The most common initial symptom was vaginal bleeding (94.91 per cent). Other symptoms were uncommon and were seen chiefly in patients with advanced disease.

7. The most common and preferred treatment was intracavitary radium followed by hysterectomy, which yielded 75.77 per cent 5 year survivals.

8. Multiple foci of radium were more efficient in sterilizing the uterine cavity of cancer than tandem applicators. The 5 year salvage of the patients who had a complete sterilization with radium (76.3 per cent) was higher than of those who had residual carcinoma (61.3 per cent).

9. The clinical stage of the disease and the histologic grade of the tumor were important factors in prognosis. Other factors which influenced end results were the age of the patient at the time treatment was initiated and the presence of any systemic disease which would shorten longevity.

10. The 5 year salvage for the last 6 years of the entire period under consideration was less than that for the preceding 10 years. This difference was due to the increase in the number of patients in the older age groups and in the number of inoperable cases (stages 3 and 4).

REFERENCES

1. Bastiaanse, M. A. van Bouwdijk. Cancer of body of uterus. J. Obst. Gyn. Brit. Empire, 1952, 59: 611–616.
2. Heyman, J. Annual Report on the Results in Treatment of Carcinoma of Uterus. Vol. 10. Stockholm, Sweden: Radiumhemmet, 1955.
3. Kimbrough, Robert A. Carcinoma of endometrium. Surg. Clin. N. America, 1954, 34: 1685–1695.
4. Novak, Emil. Gynecologic and Obstetric Pathology with Clinical and Endocrine Relations. 3rd ed. Philadelphia and London: W. B. Saunders Co., 1952.
5. Palmer, J. P., Reinhard, M. D., Sadugor, M. G., and Goltz, H. L. Statistical study of cancer of corpus uteri. Am. J. Obst. Gyn., 1949, 58: 457–467.
6. Peightal, Thomas C., and Crawford, David B., Jr. Treatment of endometrial carcinoma. Obst. Gyn., 1955, 5: 438–444.
7. Randall, J. H., Mirick, D. F., and Wieben, E. E. Endometrial carcinoma. Am. J. Obst. Gyn., 1951, 61: 596–602.
8. Scheffey, Lewis C. Diagnosis and management of uterine malignancy. West. J. Surg., 1952, 60: 144–155.
9. Waterman, George W., Raphael, Sumner I., and Moskosky, William. Carcinoma of the uterine corpus. Am. J. Obst. Gyn., 1952, 64: 1073–1082.
10. Way, Stanley. Aetiology of carcinoma of body of uterus. J. Obst. Gyn. Brit. Empire, 1954, 61: 46–58.

BODY COMPOSITION AND BODY WATER METABOLISM IN NORMAL PREGNANCY

HAROLD B. HALEY, M.D., and JOHN W. WOODBURY, M.D., Boston, Massachusetts

THE USE OF DEUTERIUM OXIDE (D_2O) to study water metabolism and appropriate methods for the analysis of deuterium in tissues are documented in recent publications by Schloerb, Solomon, Edelman, Haley, and their associates. This communication reports the use of these techniques to study certain phases of water metabolism during normal pregnancy. Repeated measurement of total body water has been done in several patients during the last 2 trimesters of pregnancy, at time of delivery, and in the puerperium. Water exchange within the body and with the environment have also been studied.

METHODS

Total body water was determined by injecting approximately 0.8 cubic centimeter of D_2O (99.8 per cent with 0.8 per cent NaCl) per kilogram of body weight. Venous blood samples were drawn at 2 and 3 hour intervals, at which time it has been shown that the D_2O is equally distributed throughout the body water. D_2O analyses were done with the falling drop apparatus and the mass spectrometer. From the D_2O equilibrium concentration the total body water was calculated according to the isotope dilution principle. It has been estimated by Schloerb and co-workers (12) that total body water determined by this method is accurate to ±400 milliliters.

A source of error is the difficulty in obtaining accurate body weights. We attempted to minimize this by weighing the subjects under similar circumstances and on the same scale at each observation. Weights taken shortly after delivery were obtained by weighing the patient on a stretcher, weighing the empty stretcher, and taking the difference as the patient's weight.

Water turnover rates were also measured. By turnover rate we mean the loss of body water through all possible routes and its replacement through all routes of ingestion. This is usually expressed as the fraction of total body water exchanged with the environment per unit time. In a relatively steady state of water balance the disappearance rate of D_2O from the blood is a measure of water turnover. Plotting this disappearance curve on a semilogarithmic scale gives a straight line, the slope of which represents the percentage of body water exchanged with the environment per unit time. This slope may be calculated from the formula:

$$\frac{\text{Ln } C_2 - \text{Ln } C_1}{T}$$

Where: C_1 and C_2 are the concentrations of serum D_2O in volumes per cent at the beginning and end of the time interval T, usually expressed in days and fraction thereof. Ln is the logarithm to the base e.

Serial plasma volume determinations were done by Charles Roby in 1 patient by the Evans blue (T1824) dye dilution method.

Body solids were derived as the difference between body weight and total body water.

OBSERVATIONS

The following studies were made: (1) Total body water was determined at 4 to 6 week intervals during the last 2 trimesters of pregnancy and during the puerperium in 3 normal women. (2) Water turnover rates

From the Departments of Surgery and Medicine, the Harvard Medical School; Dr. Burwell's Laboratory, Boston Lying-in Hospital; and the Laboratory for Surgical Research, Peter Bent Brigham Hospital.

This work was supported in part by grants from the Atomic Energy Commission to the Peter Bent Brigham Hospital, from the Upjohn Co. and Winthrop Stearns, Inc., and from the National Institutes of Health to the Harvard Medical School.

TABLE I.—SERIAL TOTAL BODY WATER DETERMINATIONS IN PREGNANCY

Patient		*Week*	*Weight, kgm.*	*TBW, L.*	*TBW, per cent*	*Solids, kgm.*
M.S.	Pregnancy	7	57.3	29.2	51.0	28.1
		14	58.4	29.8	51.3	28.6
		21	62.0	31.7	51.1	30.3
		26	62.9	31.6	50.2	31.3
		32	64.5	32.4	50.2	32.1
		36	67.4	33.8	50.3	33.5
		0*	67.4	34.8	51.6	32.6
	Postpartum	0†	62.3	31.3	50.2	31.0
		1	57.0	28.0	49.1	29.0
		8	56.8	29.5	51.9	27.3
A.O.	Pregnancy	26	61.0	34.1	56.0	26.9
		30	64.1	35.8	55.8	28.3
		34	65.7	34.6	52.7	31.1
		38	66.8	34.8	52.1	32.0
		0*	68.0	36.9	54.3	31.1
	Postpartum	0†	64.0	34.5	53.8	29.5
		3	63.7	33.7	52.9	30.0
C.H.	Pregnancy	26	56.9	31.5	55.4	25.4
		30	59.2	32.6	55.0	28.6
		34	60.9	34.5	56.7	26.4
		38	60.9	33.9	55.7	27.0
		0*	62.4	35.3	56.6	27.1
	Postpartum	8	53.7	27.9	52.0	25.8

*During labor.
†Immediately after delivery.

TABLE II.—PREPARTUM WATER TURNOVER RATES

Patient Age, yrs. Para	*Week of pregnancy*	*TBW turnover*	
		Per cent per day	*Liters per day*
R.P.	34	8.3	3.2
19			
1			
A.O.	26	8.1	2.8
15	30	8.1	2.9
1	34	7.4	2.6
	38	7.5	2.6
C.H.	26	8.0	2.5
14	30	8.1	2.7
1	34	7.5	2.6
	38	6.6	2.2
M.S.	7	6.3	1.9
26	14	8.1	2.4
1	32	7.7	2.5

Normal nonpregnant range, 5.0 to 10.0 per cent per day.

were determined in these 3 and 1 additional normal subject 1 to 4 times during pregnancy. (3) Equilibrium distribution between the water content of the mother's body and the water content of the products of pregnancy was determined in 4 subjects. (4) Five subjects (including 2 of the 3 in (1) above) had total body water determinations shortly after delivery and 1 week after delivery. (5) These 5 and 1 other subject had water turnover rates determined during the first postpartum week. (6) One subject had simultaneous total body water and plasma volume determinations during pregnancy and in the puerperium. (7) Two subjects had their losses in weight, water, and solids measured during labor and immediately following delivery.

TABLE III.—DISTRIBUTION OF D_2O IN MATERNAL AND FETAL TISSUES AND DURING LACTATION IN THE COLOSTRUM AND MILK

Patient	*Time after D_2O injection*	*D_2O, vols. per cent*			
		Maternal serum	*Fetal cord serum*	*Placental tissue H_2O*	*Colostrum or milk*
A.O.	5.5 hrs.	0.19	0.19	0.18	—
C.H.	13.5 hrs.	0.19	0.18	0.17	—
	4.0 days	0.14	—	—	0.13
M.S.	13.5 hrs.	0.12	0.13	0.13	—
M.H.*	18.0 hrs.	0.17	—	—	0.17

*Lactating, 6 months postpartum.

RESULTS

The results of serial total body water determinations in pregnant women are set forth in Table I. Figures 1, 2, and 3 show the same data graphically. These 3 patients show a similar gain in body weight, total body water, and body solids, with the water as a fraction of body weight remaining relatively constant during most of pregnancy. In all 3 patients during the last 2 to 4 weeks there is an increase in body water equal to or greater than the weight gain, with body solids remaining quite constant.

In Table II are reported prepartum water turnover rates both as percentage of total body water and as actual volume turned over per day. This latter figure may translate water turnover rates to more clinically familiar terms. None of the 3 patients in whom serial determinations were made showed significant change and all were within the normal nonpregnant range.

The determination of equilibrium times after injection and the simultaneous D_2O analyses in maternal serum, cord blood serum, placental tissue water, colostrum, and milk (Table III) indicate that all water in the mother, in the fetus, and in the other products of conception is in distributional equilibrium, and that this equilibrium is

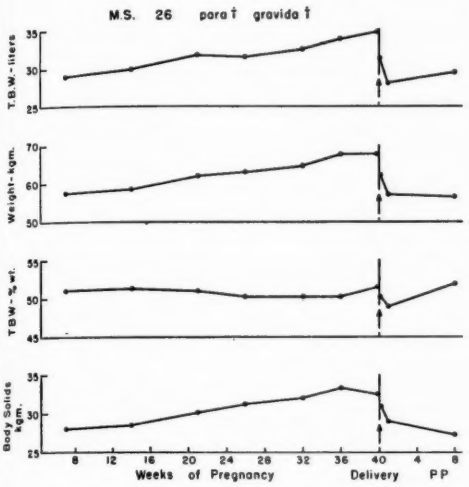


FIG. 1.

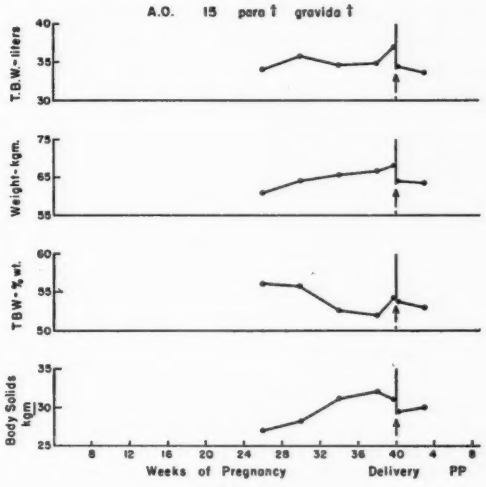


FIG. 2.

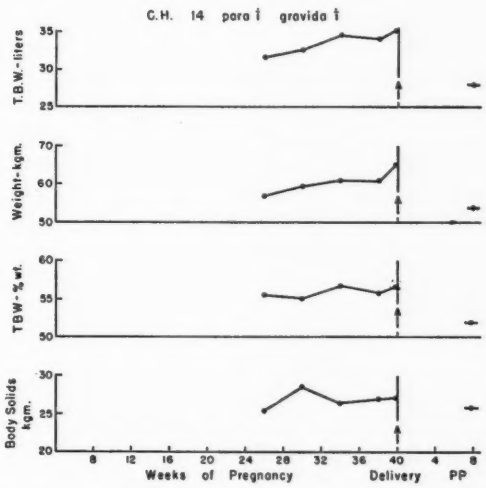


FIG. 3.

FIGS. 1, 2, 3. Serial total body water determinations on 3 patients during the last 2 trimesters of normal pregnancy and the early puerperium.

established at rates similar to those in the nonpregnant state. Additional evidence supporting this may be found in the work of Friis-Hansen and associates showing that in normal and premature newborn infants equilibrium takes place at the same rate as in adults. The work of Hellman and Flexner and their associates demonstrates such rapid transport of deuterium oxide across the placenta that the deuterium oxide space in pregnancy appears to include the water in the products of conception.

Figure 4 plots as a scattergram the figures from Table IV. Determinations of body weight, water, and solids were made within 14 hours after delivery and on the eighth postpartum day. All 5 lost body solids, and the 4 who lost weight also lost water. The 1 patient who gained weight did so by accumulating water. The solid loss in these patients varied only from 1.1 to 2.0 kilograms. With this narrow range of solid loss it is evident that change in body water is the largest factor and the largest variant in weight changes in the early puerperium.

Table V gives the turnover rates during the first 8 postpartum days in 6 subjects. One subject had a constant rate while the other 5 had a change in rate around the fourth day. Four of these 5 had turnover rates higher than the normal in the first 4 days, decreasing to normal or low normal in the next 4 days.

Figure 5 shows simultaneous total body water and plasma volume determinations on patient M. S. Note that in the thirty-sixth week of pregnancy the total body water is still rising while the plasma volume has

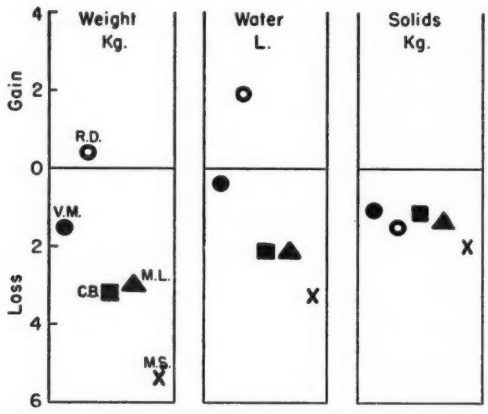


FIG. 4. Changes in body weight, water, and solids in 5 patients during the first postpartum week.

dropped significantly. This result is consistent with the findings of Caton, Roby, Reid, and Gibson.

Table VI shows weight losses in terms of water and solids during labor and at delivery in 2 subjects. This includes baby, placenta, and membranes, amniotic fluid, and blood. The first determination was made during labor and the second immediately following delivery. Since both patients had ruptured membranes prior to the first determination most of the weight loss is baby and placenta.

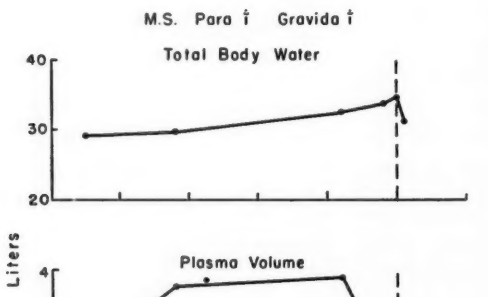


FIG. 5. Simultaneous total body water and plasma volume determinations on patient M. S.

DISCUSSION

It has been emphasized by Chesley that the changes in the maternal organism occurring during pregnancy vary widely from one woman to the next. In studying body composition in pregnancy, therefore, the most valuable information is obtained from serial determinations using the patient as her own control.

The serial body weight, water, and solid measurements on the 3 prepartum subjects show one very significant finding: namely, in these 3 normals the weight gain at the end of pregnancy is due to selective accumulation of water without significant change in body solids. The small loss of body solids in 2 of the subjects is close enough to the error of the method to require confirmation before it can be considered significant.

The early postpartum loss of body solids in the 5 patients we have studied correlates well with studies of postpartum nitrogen balance as reported by Slemons, Harding and Montgomery, Hunscher and co-workers, and Johnston and associates. These studies tend to show that a negative nitrogen balance of about 5 grams a day occurs in the first 7 days following delivery. Slemons, in 1915, found that more nitrogen was lost for a longer period of time after a conservative cesarean section than after a Porro (cesarean plus hysterectomy) operation. He thought this due to uterine involution although his hysterectomy patient lost 22 grams of nitrogen in the first 4 postoperative days before swinging into positive balance. Harding and Montgomery in 1927 determined postpartum nitrogen balances in 4 women on high calorie high protein diets. Three patients had negative balances amounting to more tissue loss than could be accounted for by the uterus. They attributed this to lactation and found that the negative nitrogen balance could not be influenced by increased calorie or protein intake.

We do not believe that either of these theories completely explains the negative nitrogen balance or the consistent postpartum loss of body solids in our patients. The

TABLE IV.—CHANGES IN BODY COMPOSITION IN THE FIRST POSTPARTUM WEEK

Patient	*Weight, kgm.*	*Water, L.*	*Solids, kgm.*
V.M.	−1.5	−0.4	−1.1
R.D.	+0.4	+1.9	−1.5
C.B.	−3.2	−2.1	−1.1
M.L.	−3.0	−1.9	−1.1
M.S.	−5.3	−3.3	−2.0

TABLE V.—POSTPARTUM TURNOVER RATES PER DAY

Patient	*First 4 days*		*Second 4 days*	
Age, yrs. *Para*	*Per cent*	*Liters*	*Per cent*	*Liters*
C.H. 14 1	8.1	—	8.1	—
V.M. 20 1	13.1	4.9	7.7	2.9
R.D. 27 2	13.4	4.5	5.5	1.9
C.B. 22 2	14.0	3.8	9.0	2.6
M.L. 18 1	10.3	3.4	7.0	2.3
M.S. 26 1	9.5	2.6	7.3	2.0

TABLE VI.—WATER AND SOLID LOSS DURING LABOR AND AT DELIVERY

	Weight loss		*Baby weight**	
Patient	*Water, L.*	*Solids, kgm.*	*Water, L.*	*Solids, kgm.*
A.O.	2.4	1.6	2.4	0.8
M.S.	3.5	1.6	2.9	0.9

*Total body water of newborn assumed to be 75 per cent body weight.

4 day negative nitrogen balance in Slemon's patient with the Porro operation, Harding and Montgomery's inability to alter the negative nitrogen balance by diet, and the constant amount of solids lost by our patients are compatible with Moore's studies showing an obligatory negative nitrogen balance for 3 to 7 days after trauma. During this period the negative balance cannot be reversed by increasing the nitrogen intake.

The selective accumulation of water at the end of pregnancy and the high rate of water turnover in the early puerperium appear to be related to certain phenomena readily observed in patients. In Stander's textbook of obstetrics the following changes in water metabolism in the early puerperium are noted: profuse sweating, increased thirst, marked increase in urinary output, and a marked increase in acetone in the first 3 days.

We have not attempted to analyze the presence or absence of a "postpartum" diuresis but our data show two phenomena that bear on this problem: namely, a consistent change in water turnover rate and a wide range of total body water changes in the first postpartum week.

SUMMARY

From the reported observations the pattern of some of the changes in body composition of the mother during normal pregnancy and early puerperium are indicated. During pregnancy, weight, water, and solids are gained. These gains are proportional until the last few weeks when there is selective accumulation of water. In the week following delivery there are profound changes in water metabolism evidenced by an elevated water turnover rate abruptly falling to normal. In the same week there is a nearly constant loss of body solids with a wide range of changes in total body water.

REFERENCES

1. Caton, W. L., Roby, C. C., Reid, D. E., and Gibson, J. G., 2nd. Plasma volume and extravascular fluid volume during pregnancy and the puerperium. Am. J. Obst. Gyn., 1949, 57: 471.
2. Chesley, L. C. Weight changes and water balance in normal and toxic pregnancy. Am. J. Obst., 1944, 48: 565.
3. Edelman, I. S., Haley, H. B., Schloerb, P. R., Sheldon, D. B., Friis-Hansen, B. J., Stoll, G., and Moore, F. D. Further observations on total body water—I, normal values throughout the life span. Surg. Gyn. Obst., 1952, 95: 1.
4. Friis-Hansen, B. J., Holiday, M., Stapleton, T., and Wallace, W. M. Total body water in children. Pediatrics, 1951, 7: 321.
5. Haley, H. B., Edelman, I. S., and Moore, F. D. The turnover rate of body water in the human. Surgical Forum 1951; American College of Surgeons. P. 595. Philadelphia: W. B. Saunders Co., 1952.
6. Harding, V. J., and Montgomery, R. C. Nitrogen metabolism in the puerperium. J. Biol. Chem., 1927, 73: 27.
7. Hellman, L. M., Flexner, L. B., Wilde, W. S., Vosburgh, G. J., and Proctor, N. K. The permeability of the human placenta to water and the supply of water to the human fetus as determined with deuterium oxide. Am. J. Obst. Gyn., 1948, 56: 861.
8. Hunscher, H. A., Hummel, F. C., Erickson, B. N., and Macy, I. G. Metabolism of women during the reproductive cycle—VI. J. Nutrit., 1935, 10: 579.

9. Johnston, J. A., Hunscher, H. A., Hummel, F. C., Bates, M. F., Bonner, P., and Macy, I. G. The basal metabolism in pregnancy. J. Nutrit., 1935, 10: 579.
10. Moore, F. D., and Ball, M. R. The metabolic response to surgery. Springfield, Ill.: Charles C Thomas, 1952.
11. Schloerb, P. R., Friis-Hansen, B. J., Edelman, I. S., Sheldon, D. B., and Moore, F. D. The measurement of deuterium oxide in body fluids by the falling drop method. J. Laborat. Clin. M., 1951, 37: 653.
12. Schloerb, P. R., Friis-Hansen, B. J., Edelman, I. S., Solomon, A. K., and Moore, F. D. Measurement of total body water in the human subject by deuterium oxide dilution. J. Clin. Invest., 1950, 29: 1296.
13. Slemons, J. M. The involution of the uterus and its effect upon the nitrogen output of the urine. Bull. Johns Hopkins Hosp., 1914, 25: 195.
14. Solomon, A. K., Edelman, I. S., and Soloway, S. The use of the mass spectrometer to measure deuterium in body fluids. J. Clin. Invest., 1950, 29: 1311.
15. Stander, H. J. Textbook of Obstetrics; designed for the use of students and practitioners. Stander's third revision. New York: Appleton-Century Co. Inc., 1945.

THE USE OF THE BIOFLAVONOID COMPOUNDS IN THE PREVENTION OR REDUCTION IN SEVERITY OF ERYTHROBLASTOSIS FETALIS

WARREN M. JACOBS, M.D., F.A.C.S., Houston, Texas

ERYTHROBLASTOSIS FETALIS is major cause of fetal loss, as well as of certain cases of cerebral palsy. Since the incrimination of the Rh-Hr system about 15 years ago as the prime factor concerned with the production of erythroblastosis fetalis, countless articles dealing with this subject have appeared. The ideal solution to this problem would be to find some substance that would either prevent this antigen antibody reaction from taking place, or prevent placental transmission of the fetal cells which initiate the reaction, or even prevent placental transmission of the antibodies themselves. To date, although many substances have been tried, nothing has been found that would accomplish any of these ends. At present the management of erythroblastosis fetalis is based upon treatment of the affected baby after delivery has taken place (1, 2). The value of exchange transfusion is well known and will not be discussed here.

THE RATIONALE FOR USE OF THE BIOFLAVONOID COMPOUNDS

The mechanism of Rh iso-immunization is based upon the concept that Rh positive fetal cells enter the maternal circulation through some break in the placental capillary system. Once these cells are in the maternal circulation antigen antibody response is set up with production of Rh antibodies. These then freely cross the placental barrier back into the fetus and attack and destroy the fetal red cells. Since the maternal and fetal bloods do not mix, it is logical to think that the fetal cells cross the placental barrier because of some break in the capillary system. Javert states that in normal pregnancy varying degrees of decidual bleeding take place. He further states that the normal conditions which cause decidual bleeding are dilatation, engorgement, and stretching of the veins to the breaking point, and trophoblastic erosion, invasion, and perforation of the decidual veins. Mengert and his associates, in working with cells tagged with radioactive iron and also using cells with sickle cell trait, have shown that in a normal pregnancy a certain small number of fetal cells gain entrance to the maternal circulation, probably through some break in the capillary system. Increased fragility in the capillary bed is a venular defect. In 5 human subjects observed with spontaneous petechia formation in the bulbar conjunctiva, Lee, Goebel, and Fulton stated that the petechia were associated with venular changes. These latter consisted of annular and saccular widening, with reduced venular blood flow velocity in the widened portion, a turbulence of blood flow, and an observed escape of red cells from this distorted segment. In most instances, it was possible to see that the walls of the venule usually had a tricornered tear through which the blood cells escaped. It is conceivable that this may be the mechanism for the escape of fetal cells into the maternal circulation. Since the bioflavonoids oppose this action it is possible that when given during the course of a pregnancy this crossover of fetal cells may be reduced or even prevented. Since the bioflavonoids have an antihistamine action, this may also be of benefit, since Rh-Hr sensitization is an antigen antibody reaction.

From the Department of Obstetrics and Gynecology, Baylor University College of Medicine, Houston.

However, it must be stated that the antihistamine drugs have been tried in the past without much success. Finally, increased capillary fragility in the baby is a prominent feature of erythroblastosis. These three factors then—prevention or reduction in capillary fragility of the placenta, antihistamine reaction, reduction or prevention of capillary fragility in the baby—are the basis for the use of bioflavonoid compounds in the treatment of Rh iso-immunized women.

MATERIAL AND METHODS

Since most Rh negative women never develop antibodies, it would be a long and almost impossible task to evaluate the results of this therapy in all such patients. In this report only mothers with previous definite evidence of immunization are used. It is generally agreed that once immunization has occurred, each additional Rh positive child will be affected, and probably somewhat more so than his predecessor. Obviously, antibodies which are already present cannot be reduced or destroyed, but it is hoped that further crossover of fetal cells and additional iso-immunization may be prevented or kept at a minimum. This report deals with 6 cases of previously Rh immunized mothers treated with CVP, the trade name of a bioflavonoid compound, during the course of their present pregnancy. Twelve such mothers received therapy with CVP, but 6 were discarded from the series, 5 because the babies proved to be Rh negative (all of these husbands were heterozygous positive), and 1 because the previous history of immunization was doubtful. The dosage of CVP used in these patients was 6 capsules daily, which consists of 600 milligrams of the bioflavonoid compound. This therapy was started before the fourteenth week of pregnancy, since it is believed that crossover does not occur prior to this time.

CASE REPORTS

CASE 1. Mrs. P. M., a 25 year old white para 1-0-0-1, was Rh negative. Her husband was heterozygous Rh positive, genotype CDE/c(d)e.

The patient had received intramuscular Rh positive blood when she was an infant. Results of titer studies made prior to her first pregnancy were as follows: blocking titer, positive undiluted strength only; agglutinating titer, negative; indirect Coomb's test, negative. Her first delivery was in January 1954. The results of titers prior to delivery in this pregnancy were as follows: blocking titer, 1 to 32; agglutinating titer, negative; indirect Coomb's test, strongly positive.

The baby was a male, weighing 6 pounds 9 ounces. Moderately severe erythroblastosis was present. He was treated by exchange transfusion. The neonatal period was essentially uneventful but secondary anemia developed about 7 days after delivery. He was treated by 2 additional simple transfusions and left the hospital about 3 weeks after birth.

The patient's last menstrual period had been on September 3, 1954 and the expected date of delivery was June 10, 1955. CVP in a dosage of 6 capsules daily was begun on October 15, 1954. Initial titer studies showed the following results: agglutinating titer, negative; blocking titer, 1 to 16; indirect Coomb's, strongly positive. Her prenatal course was essentially uneventful. At 38 weeks' gestation, results of titers were as follows: agglutinating, negative; blocking, 1 to 32; indirect Coomb's, strongly positive. Labor was induced by amniotomy on May 30, 1955, in approximately the thirty-ninth week of gestation. Delivery was performed by outlet forceps and left mediolateral episiotomy after a 6 hour uncomplicated labor.

The baby was a 6 pound 9 ounce male, in good condition. Results of laboratory studies on the cord blood were as follows: hemoglobin, 18 grams; red blood cell count, 5 million; Rh positive; direct Coomb's, positive; serum bilirubin, 3.5 milligrams per cent. The baby at this time still showed no evidence of jaundice and appeared to be a healthy infant. Exchange transfusion was done because of the patient's past history and because the baby did have a strongly positive direct Coomb's. The attending pediatrician and the obstetrician, who had also taken care of this patient and her baby during her first pregnancy, both believed that this baby was healthier than the first one and probably could have survived without an exchange transfusion. The baby had an uneventful neonatal period and left the hospital with the mother on the fifth postpartum day.

CASE 2. Mrs. H. G., a 34 year old white para 3-0-1-2, was Rh negative. Her husband was heterozygous Rh positive, genotype CDE/c(d)e.

Her first child was Rh positive with no evidence of erythroblastosis; the second child, Rh negative. Her third pregnancy terminated in a 7 month stillborn due to hydrops fetalis.

Her last menstrual period had been on September 25, 1954 with the expected date of confinement July 2, 1955. CVP in a dosage of 6 capsules daily was begun on January 1, 1955. Results of initial titer studies were: blocking titer, negative; agglutinating titer,

negative; indirect Coomb's, negative. Her prenatal course was essentially uneventful. No titer changes occurred at any time during the pregnancy, all remaining negative. Spontaneous labor occurred and delivery was made per low forceps with midline episiotomy on July 2, 1955.

The baby was a 5 pound 11 ounce female, in good condition. Laboratory studies on the cord blood were reported as follows: Rh positive; direct Coomb's test, negative; hemoglobin, 20 grams; red cell count, 5.6 million; serum bilirubin, 2.1 milligrams per cent. There was no evidence of erythroblastosis. Laboratory studies were repeated in 4 hours and there was no appreciable change. The baby had an uneventful neonatal period and left the hospital with the mother on the third postpartum day.

CASE 3. Mrs. O. W., a 31 year old white para 2-0-0-2, was Rh negative. Her husband was heterozygous Rh positive, genotype CDE/c(d)e.

Her first child was Rh positive with no evidence of erythroblastosis. Her second pregnancy terminated at 8 months with a stillborn due to hydrops fetalis.

Her last menstrual period had been on August 15, 1954 with the expected date of confinement May 22, 1955. Results of initial titers were: agglutinating titer, negative; blocking titer, negative; indirect Coomb's, negative. CVP therapy in a dosage of 6 capsules a day was begun in December 1954. Her prenatal course was essentially uneventful. No titer rise occurred at any time throughout the course of pregnancy. Indirect Coomb's test on the mother was consistently negative. Spontaneous labor occurred and delivery was on May 11, 1955.

The baby was a 6 pound 15½ ounce female with no gross evidence of erythroblastosis. Laboratory studies on the cord blood were reported as follows: hemoglobin, 16 grams; red cell count, 5.2 million; serum bilirubin, 1.6 milligrams per cent; Rh positive; direct Coomb's test, negative. Laboratory studies were repeated in 3 hours and no appreciable changes were noted. The baby had an essentially uneventful neonatal period and left the hospital with the mother on the third postpartum day.

CASE 4. Mrs. D. N., a 37 year old white para 7-0-0-7, was Rh negative. Her husband was homozygous positive, genotype CDE/C(D)E.

The first 5 children were apparently all normal with no evidence of erythroblastosis. During the sixth pregnancy, the blocking titer rose to 1 to 32 prior to delivery, and a positive indirect Coomb's was also obtained on the mother at this time. The baby had moderately severe erythroblastosis and was treated with exchange transfusion resulting in an uneventful neonatal period. During the seventh pregnancy the blocking titer also rose to 1 to 32, and a positive indirect Coomb's was also obtained on the mother prior to delivery. This child also had a moderately severe erythroblastosis with a strongly positive direct Coomb's test. Treatment of the infant was with exchange transfusion. The baby had an essentially uneventful neonatal period.

Her last menstrual period had been on February 19, 1955. The expected date of confinement was November 26, 1955. CVP therapy of 6 capsules a day was begun on May 17, 1955. Results of initial titers were as follows: agglutinating, negative; blocking, negative; indirect Coomb's, negative. Her prenatal course was essentially uneventful. No titer rise occurred during pregnancy. Spontaneous labor was uncomplicated and delivery was on November 21, 1955.

The baby was an 8 pound 7 ounce male, in good condition, with no gross evidence of erythroblastosis. Laboratory studies on cord blood were reported as follows: hemoglobin, 17 grams; red blood cell count, 5.7 million; Rh positive; direct Coomb's test, negative; serum bilirubin, 4 milligrams per cent. Laboratory studies were repeated 3 hours later with no appreciable change. The baby had an essentially uneventful neonatal period and left the hospital with the mother on the third postpartum day.

CASE 5. Mrs. F. L., 26 year old white para 3-1-0-2, was Rh negative. Her husband was heterozygous Rh positive, genotype CDE/c(d)e.

Her first child was normal with no evidence of erythroblastosis. The second child had severe erythroblastosis. The child was treated with exchange transfusion and survived after a stormy neonatal period. One spontaneous abortion occurred at 2 months following this second pregnancy.

Her last menstrual period was on October 9, 1954. The expected date of confinement was July 16, 1955. CVP therapy in the dosage of 6 capsules a day was begun early in January 1955. Initial titer studies showed: agglutinating titer, negative; blocking titer, 1 to 8; indirect Coomb's, strongly positive. Her prenatal course was essentially uneventful. At the thirty-sixth week, results of the titer studies were as follows: blocking titer, 1 to 16; agglutinating titer, 1 to 2; indirect Coomb's, strongly positive. Labor was induced with pitocin on June 20, 1955, and spontaneous delivery with midline episiotomy was accomplished after an uncomplicated 6 hour labor.

The baby was a 4 pound 12 ounce female in good condition, with no gross evidence of erythroblastosis at birth. Laboratory studies on the cord blood were reported as follows: hemoglobin, 19 grams; red blood cell count, 5.8 million; Rh positive; direct Coomb's, strongly positive; serum bilirubin, 6.3 milligrams per cent. Because of the past history of this patient and because of the strongly positive direct Coomb's test, exchange transfusion was done. The baby had an essentially uneventful neonatal period and left the hospital with the mother on the fourth postpartum day. It was the opinion of both the attending pediatrician and the obstetrician, who had also taken care of this patient in her last pregnancy, that this baby was less affected than the last one, and could probably have survived without an exchange transfusion.

CASE 6. Mrs. A. S., a 29 year old white para 4-0-0-4, was Rh negative. Her husband was heterozygous Rh positive, genotype CDe/c(d)e.

Her first 3 babies apparently were unaffected. The fourth baby was a severely erythroblastotic infant, who was treated with exchange transfusion and survived after a very stormy neonatal period. The blocking titer just prior to delivery in this pregnancy was 1 to 512, and a strongly positive reaction to an indirect Coomb's test was obtained on the mother at this time.

Her last menstrual period was on December 24, 1954. The expected date of confinement was October 1, 1955. Therapy with CVP in a dosage of 6 capsules a day was begun on February 1, 1955. Initial titer studies showed: blocking titer, 1 to 256; agglutinating titer, negative; indirect Coomb's, strongly positive. Her prenatal course was essentially uneventful. At the thirty-seventh week titer studies were reported as follows: blocking, 1 to 512; agglutinating, negative; indirect Coomb's, strongly positive. Spontaneous labor was uncomplicated and delivery occurred on September 22, 1955.

The baby was a 7 pound 8 ounce female, in good condition, with no jaundice noticed at birth. Laboratory studies on cord blood were reported as follows: Rh positive; direct Coomb's, weakly positive; hemoglobin, 20 grams; red blood cell count, 5.4 million; serum bilirubin, 5.0 milligrams per cent. Because of the past history, and because the baby had a positive Coomb's, an exchange transfusion was done. The baby had an uneventful neonatal period and left the hospital with the mother on the fourth postpartum day. It was the opinion of both the pediatrician and the obstetrician, who had taken care of this patient in her last pregnancy, that this baby was a healthier baby and less affected than her predecessor.

DISCUSSION

The seemingly most dramatic results were obtained in Cases 2, 3, and 4. These patients, although having delivered erythroblastotic infants before, showed no titer rise throughout their pregnancies, and the present infants were completely unaffected, as evidenced clinically and by laboratory studies. In Cases 1, 5, and 6, base-line titers were present early in gestation, which apparently represented holdover antibody titers from previous immunization. In all of these the titer rise was only slight. One would expect that under ordinary circumstances these infants would be at least as severely affected as their predecessors, and probably more so. However, it was the opinion of the attending physicians in all of these cases that these infants were healthier and less affected than the previous ones. These infants received exchange transfusion because it would not be fair to compromise the current principles of therapy of erythroblastosis fetalis on the basis of an unproved drug, but it was believed by all concerned that because these infants were only mildly affected exchange transfusion probably was not necessary. It would be rather presumptuous to forecast a cure-all for erythroblastosis fetalis on such a short series of cases. However, based on these cases, there is evidence that the bioflavonoid compounds do have some value in the prevention or reduction in severity of erythroblastosis fetalis. Only similar studies with larger series of cases such as these will give the ultimate answer, and such studies are now being undertaken. For the present time, however, it must be emphasized that the best available treatment of erythroblastosis fetalis is the proper timing of delivery and exchange transfusion in the newborn infant. These principles should not be put aside in favor of an, as yet, unproved drug.

REFERENCES

1. JACOBS, W. M. Modern concepts in the management of the Rh negative obstetrical patient. Med. Rec., Houston, 1955, 49: 422.
2. JACOBS, W. M., and KOHN, M. I. Erythroblastosis fetalis; a review of 73 cases. Obst. Gyn., in press.
3. JAVERT, C. T. Decidual bleeding in pregnancy. Ann. N. York Acad. Sc., 1955, 61: 637.
4. LEE, R. E., GOEBEL, D., and FULTON, T. A. Anatomical and functional change in the peripheral vascular system during certain induced increases in vascular fragility. Ann. N. York Acad. Sc., 1955, 61: 660.
5. MENGERT, W. F., and associates. Placental transmission of erythrocytes. Am. J. Obst. Gyn., 1955, 69: 678.

EDITORIALS

THE "CURATIVE" RESECTION—A PREFERRED STATISTICAL UNIT FOR EVALUATING THERAPY IN CANCER OF THE STOMACH

STANLEY O. HOERR, M.D., F.A.C.S., Cleveland, Ohio

IN THEIR EFFORTS to improve the results of treatment of cancer of the stomach, surgeons have used two approaches: they have operated upon a larger proportion of all patients who have the disease, and they have performed operations of greater magnitude. These efforts unexpectedly have led to a statistical emphasis on "operability" and "resectability" rates. These rates now are outmoded because of the ambiguous way in which they may be utilized. Any willing patient may be operated upon and his case statistically included in the operability rate, regardless of whether the operation benefits him. Likewise, any patient with malignant gastric disease may have the stomach resected and thus be statistically included in the resectability rate—regardless of the amount of tumor removed or left behind and regardless of the possible disservice that the resection may prove to be to the patient with a hopeless prognosis.

The operability rate has little value in comparing results between different institutions. It may be of some value as an index of the co-operation between the internist and the surgeon, but surely the emphasis in obviously hopeless cases should be on tissue diagnosis that is obtained without laparotomy when possible. On the other hand, the resectability rate (which by definition includes potentially curable as well as incurable lesions) measures nothing that is useful and confuses analyses of the long-term results.

The 5 year survival rate of all patients who have had a diagnosis of cancer of the stomach has no validity when used in a comparison of results between institutions having nonuniform patient populations. For example, a charity institution undeniably tends to have a much lower proportion of patients with potentially curable gastric cancers, and may report such a 5 year survival rate of less than 5 per cent. The private clinic, on the other hand, tends to have a higher proportion of patients with favorable cancers and may report a 5 year survival rate of more than 15 per cent. The implication that more effective surgery is performed in the institution boasting the higher rate is therefore unproved because the factor of patient population is not considered in the operability rate.

Inasmuch as progress in the treatment of cancer depends upon a pooling of the experiences of many different individuals, a more precise basis (than that of operability or resectability) for comparing results is essential. It is suggested that patients with gastric cancer be classified into two fundamental groups: (1) patients in whom the

From the Department of General Surgery of The Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute.

lesion is incurable by surgical means, either by reason of distant metastases, or by virtue of local extension beyond the limits of possible removal; (2) patients in whom the lesion apparently is curable by surgical means, and at operation all gross evidence of malignancy is removed. These groups may then be considered from two important aspects of therapy: (a) the results of palliative treatment of grossly incurable lesions, (b) the results of resections of lesions that grossly appear to be curable. Refinements in the classification of lesions that appear to be curable will suggest themselves—carcinoma must be differentiated from lymphoma and sarcoma; lesions with metastases to regional nodes should be in a separate category from those without metastases; lesions requiring resection of multiple organs should be in a separate category from those confined to the stomach. But these are only refinements in the statistical picture. In assessing the results of surgical treatment of cancer of the stomach, let us scrupulously differentiate the apparently curable lesions from the obviously incurable lesions. Let us abandon the outmoded classifications of "operable" and "resectable" and base our assessments on whether a "curative" resection has been performed.

AN AVERAGE SURGEON COMPLAINS

KENNETH B. CASTLETON, M.D., F.A.C.S., Salt Lake City, Utah

IT IS NOT AN UNCOMMON EXPERIENCE for a general surgeon in private practice to read or to hear an account by a prominent surgeon of national repute regarding a new surgical procedure or technique, to try out the procedure on the basis of a favorable report only to find that the later results are not as favorable as the immediate results would indicate, and on investigation to discover that the procedure has already been discarded by those who introduced it without an adequate report of the failures. This, to my mind, constitutes one of the great faults and defects of current surgical literature. The fault is really multiple. First, it would appear that, in many instances, there is too great haste in reporting new developments and procedures whose values are not proved. Secondly, there seems to be a reluctance or, at least, a tardiness, on the part of some surgeons to report their unfavorable results and to reverse their previous stand regarding a procedure, so that by the time the failure of the procedure is known to a surgeon in the "grass roots" area much harm may already have resulted from its use. If the surgeon who first reported the procedure would be in as great a hurry to report his poor results as he was in his initial report, much of this difficulty could be avoided.

At present, there is a good deal of confusion regarding the surgical treatment of peptic ulcer. Thirty years ago the standard operation for duodenal ulcer requiring surgery was gastroenterostomy. Later, it became apparent that there was a considerable incidence of recurrent ulcer and almost at once there was a swing toward gastric resection. When it became apparent later that there were some recurrences following gastric resection the cry immediately went up for more radical resections. Soon it became apparent that a good many patients who were subjected to very radical resections were suffering from side effects of the operation, especially the dumping syndrome and loss of weight, although cured of ulcer disease. These side effects may vary all the way from a slight annoyance to a severity which converts the patient into a gastric cripple who is unable to work and support himself and his family. In an attempt to solve this problem, a variety of procedures have been proposed. We now have gastric resection combined with vagotomy, segmental gastric resection, gastroenterostomy with vagotomy, staged procedures starting with conservative ones such as gastroenterostomy and later subjecting the failures to further surgery, usually more radical in nature, and also Billroth I operations with and without vagotomy. The average surgeon now may well be confused as he faces the problem of which procedure to carry out in a given case. A case in point is the Billroth I operation for duodenal ulcer. Many surgeons have become much interested in this procedure in recent years and are using it with great satisfaction in many cases of gastric ulcer and gastric carcinoma. Others are using it with apparent satisfaction for duodenal ulcer although there is some evidence in the literature which would suggest that the recurrence rate in cases of duodenal ulcer may be higher than in cases in which the more conventional Billroth II modifications were performed. There are a number of surgeons who have had wide experience with Billroth I operation for duodenal ulcer. These men should study their results in duodenal ulcer carefully and in the next few years should make full, honest, objective reports in the surgical literature, which would settle once and for all the question of recurrence. Meanwhile, it would seem wise for the others to go a

little slowly on the Billroth I procedure for duodenal ulcer, and for the time being to use it only in gastric ulcer and gastric carcinoma if they choose to use it at all. The same general policy would seem to be advisable in segmental gastric resection and in conservative gastric resection combined with vagotomy. Again, with these procedures and with many others, it would seem wise for the few surgeons who are interested in these procedures, and who are in a position to study sizeable groups, to study them carefully and, from time to time, report on the follow-ups as the years go by. In this connection it would seem desirable for surgeons in large clinics and large university surgical centers to combine their efforts and to make co-operative studies and reports on their experiences in an effort to settle these matters completely. This would appear to be a much better plan than cluttering up the surgical literature with the reports of many surgeons of limited experience with only short time follow-up studies.

Although the problem has been presented only as it relates to gastric surgery, exactly the same line of reasoning could be applied to many other procedures, such as surgical treatment of carcinoma of the breast. Ten years ago we could proceed with confidence with radical mastectomy for carcinoma in cases which fulfilled the criteria for operability. Now we are confused. Should we do the standard radical mastectomy? Should we remove the internal mammary nodes? Should we do one of several extended or superradical mastectomy procedures? Although it is realized that it will take years to settle these problems, it would seem highly desirable, as noted before, for a few men who are interested in them to evaluate their results carefully and make reports from time to time. Meanwhile, the rest of us might do well to adhere to the standard procedures until sufficient reports on the new procedures are available to evaluate them properly. Obviously, there would be certain exceptions to this policy. If a new procedure should appear to offer unusual promise of superior results, it might seem highly desirable for the investigator to report it as soon as possible in order that lives might be saved without waiting for long term follow-ups even though it is acknowledged that the latter might alter the original favorable outlook somewhat. This would apply only to exceptional procedures however.

Finally, it is acknowledged that this "grass roots surgeon" is often at fault in adopting surgical procedures on the basis of preliminary reports and without adequate studies and follow-up reports. Undoubtedly, many such surgeons are quick to adopt any procedures on the basis that they are keeping up-to-date, keeping ahead of their competition, establishing a reputation for being modern, up-to-date surgeons, instead of adopting the wiser course and waiting until the new procedure can be properly evaluated in the light of more time and experience.

In summary I would like to complain about some aspects of current surgical literature as follows: (1) Many surgeons report new procedures and techniques prematurely. (2) There seems to be a reluctance and a tardiness on the part of many surgeons in reporting poor results. (3) Many general surgeons are too hasty in trying out newly reported procedures. (4) A plea is made for more co-operative and combined studies on controversial surgical problems by large surgical institutions.

THE SURGEON AT WORK

THE USE OF RAYON MESH IN SKIN GRAFTING AND GRANULATING WOUNDS

PATRICK C. SHEA, JR., M.D., F.A.C.S., WILLIAM A. REID, M.D., and
ALBERT H. WILKINSON, JR., M.D., Atlanta, Georgia

THE MOST IMPORTANT PREREQUISITES for satisfactory wound healing are: prevention of the accumulation of blood, serum, or other liquid materials, proper coaptation of wound edges, and avoidance of infection. These factors apply particularly to cases involving a great deal of reconstruction, such as repair of granulating areas resulting from burns and chronic leg ulcers. The use of a rayon mesh, nonadherent dressing by the technique to be described has produced the most favorable results.

MATERIAL

The nonadherent dressing consists of a continuous rayon filament knit into a fabric which has dimensional stability lengthwise for easy handling and is distensible, crosswise and on the bias, for conformability (Fig. 1). Its mesh permits rapid drainage of the wound exudate into the secondary dressing, and thereby precludes maceration. The emulsion impregnant does not block the open mesh of the fabric but is confined to the threads, rendering them nonadherent. At the same time, the composition is such that it encourages transfer of the exudate to the overlying, absorbent dressing. The impregnant is neither heavy nor greasy.

The mesh dressings measure 3 by 8 inches and come 3 to a package, autoclaved and ready for use. For maximum protection they are sealed in airtight and watertight aluminum foil.

From the Whitehead Department of Surgery, Emory University, Emory University, Georgia, and Grady Memorial Hospital, Atlanta.

In the series of cases reported here, rayon mesh was used as the initial dressing layer following skin grafting procedures and in the redressing of granulating wounds.

METHOD

A. *Skin grafting procedure.* After split thickness skin grafts, either in sheet or postage stamp form or as pinch grafts, had been applied, one thickness of rayon mesh was overlaid smoothly and compressed firmly. The edges were sutured at ½ to ¾ inch intervals with No. 0000 silk, preferably into normal skin (Fig. 2). In a large graft area, the sutures necessarily were inserted through mesh, graft, and into the granulation bed for retention. Suturing the mesh dressings in place proved important in achieving good results. Dry dressings of fluffed-out gauze, with other flat gauze dressings, were then superimposed in that order.

The rayon mesh was similarly applied and sutured over donor areas and overlaid with a dry dressing. The mesh was removed from the graft areas on the eighth postoperative day and from the donor sites in 10 to 14 days.

This method was used in 17 patients, who required skin grafts—and, in several instances, staged grafting procedures—for reconstruction of burned areas; in 5 patients with grafts following radical mastectomies; and in 1 with a skin graft of the face.

B. *Onlay surgical dressings.* Rayon mesh as the initial layer with dry dressings superimposed was used for chronic leg ulcers and in the re-

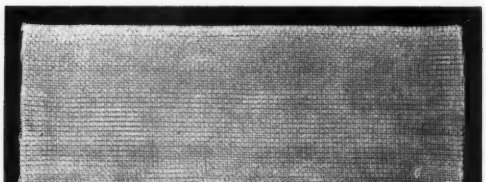


FIG. 1. Nonadherent dressing of rayon filament mesh.

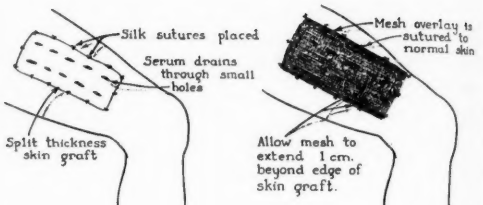

Silk sutures placed
Serum drains through small holes
Split thickness skin graft
Mesh overlay is sutured to normal skin
Allow mesh to extend 1 cm. beyond edge of skin graft.

FIG. 2. Application of split thickness graft with mesh overlay.

dressing of other granulating wounds (e.g., third degree burns undergoing staged grafting procedures).

In 14 patients with chronic leg ulcers, 189 applications of rayon mesh were used as the initial layer of the dressings. In addition, onlay mesh dressings were used on innumerable burn wounds while they were being prepared for grafting, or between procedures when grafts were done in stages.

RESULTS

In group A (skin grafting procedures), the results were uniformly satisfactory, with a minimum of 95 per cent "take" in each instance. This dressing technique was observed to have many advantages over the other types previously employed, namely: (1) Superimposed dry dressings were changed frequently without disturbing donor sites, thus achieving healing without interference and avoiding maceration and the collection of fluid under the healing graft. (2) The mesh remained soft and nonadherent during the period it was in place. (3) All dressings, including the rayon mesh, were removed easily, painlessly, and with no loss of tissue. (4) Because granulations do not stick to the mesh, its removal left them undisturbed and did not cause bleeding. (5) The pliability and softness of the mesh added to the patients' postoperative comfort.

In 3 cases of reconstruction of denuded burned areas, in which moistened saline gauze sponges were applied as a stent-type dressing, some maceration in the wound and sticking of the mesh occurred.

In group B patients, who had onlay mesh dressings and who experienced repeated dressing changes in granulating wounds, objective and subjective observations were gratifying. The patients consistently noted that dressings could be changed without pain. It was also observed in evaluating results that infection was lessened, no maceration occurred, epithelialization was not interfered with, and no allergic tendencies were evident. Drainage through the interstices of the mesh into the superimposed dry dressing resulted in a more satisfactory wound; the granulations remained fresh, firm, as well as young in appearance.

DISCUSSION

Interest in the type of dressing described was derived from a clinical study covering a 3 year period (3). During this time, 42 children with old and recent burns in various stages of delayed healing were referred to a medical center for treatment. Effective techniques in dressing and reconstitution of old, infected, granulating wounds were of paramount importance in rehabilitating these patients both from the standpoint of decreasing morbidity and severe economic stress.

Although techniques for suturing dressings in place have been described by Brown and McDowell and utilized by surgeons, especially in plastic and reconstructive surgery, their merits have failed to find the popularity they deserve among surgeons generally.

Nagle, in 1948, using a different type of suture dressing, very ably described the goal sought. He stated: "It is important that blood serum and pus drain freely through the meshes of the grease gauze dressing, to be absorbed by the overlying compressed gauze. Additionally, it is important that the dressings overlying a skin transplant may 'breathe,' that is to say, that the liquids absorbed by the gauze may evaporate into the atmosphere. If this function is not served by the dressing of the skin transplant, it will frequently macerate and undergo leucocytic digestion."

That goal is achieved through the use of rayon mesh by the technique described in this report. The incorporation of rayon into surgical dressings is not new. The advance lies in the use of rayon mesh as the initial layer of dressing with a superimposed dry dressing.

In addition to the advantages previously mentioned, it was noted: (1) In freshly débrided wounds in which immediate reconstitution was not practicable, the application of mesh helped produce a more satisfactory wound for later grafting procedures; when infection was rampant, topical antibiotics in dry or moist vehicles could be applied and beneficial results obtained; and drainage material could be removed without disturbing the granulating bed simply by changing the overlying dry dressing. (2) In known "keloid formers" the tendency to reform keloids was lessened when new grafts were applied. (3) In this study, only a few specific types of wounds were under consideration; it is suggested that the use of rayon mesh be explored for its value in other situations.

SUMMARY

1. A nonadherent rayon mesh dressing is described.

2. Its application and value are demonstrated in this clinical research study.

3. No allergic or toxic reactions resulted from its use.

REFERENCES

1. Brown, James Barrett, and McDowell, Frank. Skin Grafting. 2nd ed., pp. 85–93. Philadelphia: J. B. Lippincott Co., 1949.
2. Nagle, P. S. Onlay gauze pressure dressing. Surgery, 1948, 24: 1016–1019.
3. Shea, P. C., Jr., and Robertson, Roy L. Unpublished data.

THE USE OF CONTINUOUS NEGATIVE PRESSURE AFTER LARYNGECTOMY AND RADICAL NECK DISSECTION

F. JOHNSON PUTNEY, M.D., Philadelphia, Pennsylvania

BORROWING from the general surgeon's use of continuous negative pressure after radical mastectomy which resulted in faster healing without fluid collection or marginal skin necrosis, this method was employed during the past year in 36 cases of laryngectomy and radical neck dissection alone, or in combination. Its postoperative use in 11 cases of laryngectomy, 9 cases of radical neck dissection, and 16 cases of combined laryngectomy and neck dissection proved highly successful. Even in the patients who had received previous irradiation therapy, healing was prompt and without complication.

A striking example was a patient who had a thyroidectomy for carcinoma of the thyroid gland followed by intensive irradiation therapy to a large mass of metastatic lymph nodes, a total of 9,000 roentgens being administered to the thyroid area. The irradiation was begun 2 weeks after surgery, but the reaction was so severe that the original incision ruptured and healed with much difficulty. Prior to this treatment, it seemed improbable that the entire metastatic carcinomatous mass could be removed, but, after irradiation, reduction in size rendered surgery feasible. Six months later, a radical neck dissection was performed and continuous suction drainage was applied to the neck. The wound healed by first intention within a week with no sloughing.

Prior to the use of continuous suction, dependent drains were placed in the neck and firm dressings applied, but it was difficult to obtain sufficient pressure by this means to obliterate the remaining dead space completely. Tight dressings not only constricted the vascular supply in the neck but, after radical neck dissection when the larynx and trachea were undisturbed, also produced pressure on the airway. After removal of the larynx the wounds commonly healed by primary intention until the fifth or seventh day when breakdown with purulent drainage developed in some cases, increasing the length of hospitalization and the incidence of pharyngeal fistula formation. The purulent discharge was attributed to pocketing of serum without proper elimination by static drainage so that secondary infection and necrosis followed. In some instances the skin flaps exhibited a red and edematous appearance from the subsequent infection.

For laryngectomy a midline incision was used (Fig. 1), and for combined laryngectomy and

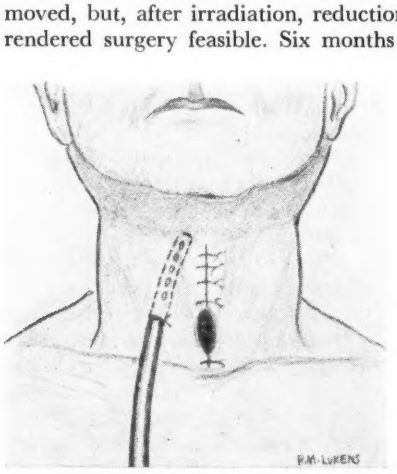


FIG. 1. Position of catheter for drainage after laryngectomy.

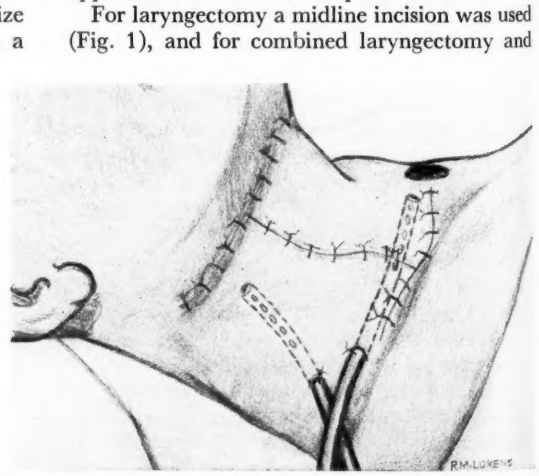


FIG. 2. Drainage with lateral H shaped incision after combined laryngectomy and radical neck dissection.

TABLE I.—DRAINAGE AFTER LARYNGECTOMY

Case No.	24 hrs., c.c.	48 hrs., c.c.	72 hrs., c.c.	Remarks
1	100	50		
2	50	20		
3	200	30		Post radiation
4	100	30		Post radiation
5	50	20		Post radiation
6	100	40		Post radiation
7	140	40		
8	150	100	50	
9	100	100		
10	120	80	20	
11	100			
Average	110	46	6	

TABLE II.—DRAINAGE AFTER COMBINED LARYNGECTOMY AND NECK DISSECTION

Case No.	24 hrs., c.c.	48 hrs., c.c.	72 hrs., c.c.	Remarks
1	100	200		
2	120	100		
3	100	50		
4	150	60		
5	340	60		
6	150	25	75	
7	135	15		
8	150	50		Post radiation
9	150	60		Pharyngeal fistula Required plastic closure
10	100	75		
11	100	50	15	
12	75	30		External carotid artery removed
13	100	87	52	
14	50	30		
15	50	50		Pharyngeal fistula with spontaneous closure in 1 week
16	250	35	15	
Average	133	61	9	

neck dissection either an H shaped incision over the side of the neck (Fig. 2) or a wide arm Y incision. In radical neck dissection, 2 types of incisions were employed, one a double armed Y incision with flaps at both the upper and lower ends (Fig. 3) and the other a Z shaped incision (Fig. 4). The latter was preferred because of the improved cosmetic appearance, but as far as healing was concerned no difference was noted. The pharynx was closed transversely in all cases in which the larynx was removed.

After laryngectomy or radical neck dissection, a unilateral stab wound was made in the inferior posterior portion of the skin flap through which a No. 12 F. catheter with several lateral openings in the distal end was inserted to the upper angle of the wound. After combined laryngectomy and radical neck dissection 2 catheters were employed, one reaching to the angle of the jaw and lying dependent in that position and the other extending medially to the tracheal stoma. The skin flaps were tightly closed to prevent leakage, and vaselinized gauze was placed over the wound edges to seal them and eliminate sucking of air when negative pressure was applied. Only a light dressing was applied since firm pressure impeded the escape of fluid through the drainage channel. Continuous negative pressure was maintained by attachment of the catheter or catheters to a Wangensteen apparatus for at least 48 hours. After 24 hours the catheter, which could easily be felt underneath the skin, was moved about to break up light adhesions and loosen retained serum. The tube was removed at the end of 48 hours provided the drainage for the past 24 hours did not exceed 30 cubic centimeters. The serosanguineous drainage in 24 hours averaged 110 cubic centimeters after laryngectomy (Table I), 133 cubic centimeters

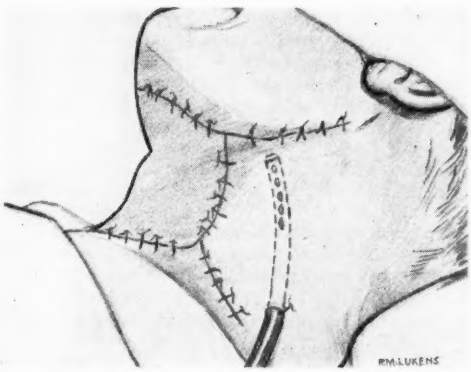


FIG. 3. Position of catheter for drainage using double Y shaped incision for radical neck dissection.

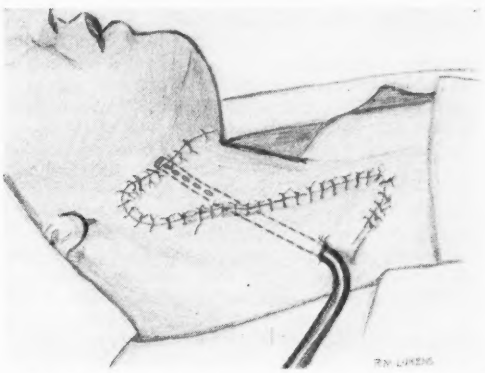


FIG. 4. Position of catheter for drainage using Z shaped incision for radical neck dissection.

TABLE III.—DRAINAGE AFTER NECK DISSECTION

Case No.	*24 hrs., c.c.*	*48 hrs., c.c.*	*72 hrs., c.c.*	*Remarks*
1	250	50		Second side
2	100	50	25	Second side
3	120	10		
4	140	75	60	Second side
5	120	15		
6	100	110	150	
7	275	125	50	Postoperative bleeding from superior thyroid artery
8				Drainage not measured
9	150	60		
Average	155	62	41	

after combined laryngectomy and neck dissection (Table II), and 155 cubic centimeters after neck dissection (Table III). At the end of 48 hours, the drainage for laryngectomy averaged 46 cubic centimeters, after neck dissection 62 cubic centimeters, and after combined laryngectomy and neck dissection 61 cubic centimeters. After the drainage catheters were removed no further aspiration of fluid has been needed.

The main complication encountered was the development of 2 fistulas, only 1 of which required secondary closure, while the other closed spontaneously within 5 days. In 3 cases there was slight necrosis of the angle of the skin wound which healed without delay. In 1 case, postoperative bleeding from the superior thyroid artery necessitated reopening of the wound on the same day as the operation and religating the artery.

SUMMARY

Continuous suction drainage was used postoperatively after laryngectomy, radical neck dissection, and combined laryngectomy and neck dissection in 36 cases. Pooling of secretion beneath the skin flaps with secondary infection and breakdown of the wound was prevented, and both the length of hospitalization and the development of pharyngeal fistulas have decreased.

THE SURGEON'S LIBRARY

Reviews of New Books

FOR THE PHYSICIAN OR SURGEON caught in the toils of practice, "keeping up" with scientific advances even in his immediate field is, under prevailing conditions, a counsel of perfection. The practitioner who highly resolves to dedicate mythical time to this objective soon falters before the impossible task of extracting the particular things he needs from a bewildering collection of repetitious articles in dozens of separate publications. He knows well that any year, any month, there may be a development in basic science that could be of practical, or at least suggestive, use in his day's work, but, as one practitioner puts it, he has not the energy, the time, or the "brain space" to continue so taxing a search.

These premises underline my discussion here of the American Foundation's two volumes, *Medical Research: A Midcentury Survey*.[1] I know of no other single source in which physicians and surgeons, whether in practice, in teaching, or in research, may acquire such an accurate, panoramic view of the fundamental research which is daily altering perspectives in their own fields. It is difficult, as one of my colleagues observed in the *Journal of Bone and Joint Surgery*, to deal with these volumes without superlatives; they "will save the would-be researcher reams of correspondence and miles of travel." Certainly they can save the practitioner many hundred hours of wandering through a miscellaneous literature.

I have been in somewhat close touch with the American Foundation's intensive 15 year study, the results of which are now concentrated in these two volumes, and I agree with the London *Lancet's* editor that these volumes are likely to "have as much influence on American medical research as Flexner's reports of 40 years ago had on American medical education." The survey carries the enthusiastic endorsement of 26 leading basic scientists and clinicians, who, as a Committee of Consultants, join the American Foundation's member-in-charge, Esther Everett Lape, in presenting it.

While the volumes make no compromises in the direction of "popularization," they are the reverse of formidable. The *New York Times* reviewer found "nothing in these two volumes that any intelligent person cannot understand." They have the unity that comes from scientific mastery of the content, from integrated thinking, and from artistic presentation. While the report is an encyclopedic synthesis of information gathered from many sources, it has the smoothness and lucidity of a single brilliant author.

Publication of the book coincides with a new evolutionary trend in the public concept of basic research. The trend is manifest in the President's messages of the current year, followed by a marked budgetary stepping up of funds for medical research "including basic research." Hitherto, provision for medical research has been dominantly influenced by the idea (completely assimilated by Congress) that every separate "disease" requires an especial line of investigation. Hence the separate institutes and the separate "drives" for cancer, poliomyelitis, heart disease, arthritis, and multiple sclerosis. Yet the investigator knows —and the public and government are beginning to realize—that the same broad currents of basic research underlie the problems of most or all "diseases"; also that the basic research that will pay the highest dividends is the research that aims at elucidation of fundamental causes rather than discovery of specific remedies. The best therapeutic agents we now know are still nonspecific; as basic research into mechanisms develops, they become less and less empiric.

The understanding of all disease and the possibility of substituting rational for empiric therapy, as the American Foundation's study concretely shows, imply research in molecular biology, including all aspects of the life and activity of single cells, of specialized cells within the complex body, organized body, or of the organism reacting as a whole through integrated and adapting mechanisms. This concept completely challenges the ancient error of attributing disease to single factors. It reflects realization that a change in even one molecule may reverberate throughout the entire system, producing changes in seemingly unrelated organs and tissues. In the light of this truth, every disease, however localized or however specific its manifestations, must be dealt with as a generalized condition, and concentration of research upon the end results of a chain reaction becomes a dubious procedure.

These concepts, as *Medical Research* at various points implies, are as pertinent to surgeon as to physician. The popular tendency to ascribe the miracles of modern surgery to technical feats is not borne out by his-

[1] MEDICAL RESEARCH: A MIDCENTURY SURVEY. Published for The American Foundation, New York. Vol. I. American Medical Research: in Principle and Practice. 765 pages. Vol. II. Unsolved Clinical Problems: in Biological Perspective. 740 pages. 2 volumes, $15.00. Boston and Toronto: Little, Brown & Co., 1955.

tory. The miracles derive rather from the surgeon's increased preoccupation with physiologic mechanisms. Even the most highly developed surgical techniques—as new methods for clearing the operative field in cardiac surgery, for maintaining the circulation and oxygenating the blood—illustrate the truth that mechanics can go so far and no further. Mechanical devices for maintaining any one function cannot transcend the fact that the given function is part of a living organism, *all* parts of which are the surgeon's concern. The development of intracardiac surgery (as at Harvard and in the Children's Hospital) has sometimes involved intimate collaboration of members of departments of medicine and of surgery in exploring, for instance, the physiologic changes associated with congenital defects of the heart. In some half dozen leading surgery departments of the country, new surgical techniques (artificial cardiac valves, production of shunts around stenosing valves, ways of investigating the fate of grafted blood vessels) have finally resulted from long term, fundamental investigations of physiologic mechanisms.

The developing physiologic knowledge that has led to advances in many forms of surgical procedure includes studies of the mechanisms of immunochemistry, profound work in cellular biology, physical and chemical studies of connective tissue, study of the mechanisms of action of chemicals, including hormones, on enzyme reactions. Advances in tissue homotransplantation—of skin, bone, kidney, cornea, blood vessel—derive from basic work that has been going on for years in embryology, endocrinology, genetics, cancer, nutrition, and in wound healing and other problems. The rapid advances in skin grafting during the war brought into sharp focus the problem of collapse of the vascular connections between the graft and its host bed and the death of the graft. The whole discipline of general immunology is involved in discovering the nature of the immune response of the recipient to transplanted tissues of all kinds, and the means of stimulating acquired tolerance. Pertinent also, in the highly differentiated tissues with which surgeons must be concerned, is the problem of the amazing specificity of proteins, blood proteins in every transfusion, all manner of tissue proteins. The protein problem in surgery, indeed, brings us squarely up to the need of further basic research to elucidate the still unknown structure of proteins, upon which, as Linus Pauling put it, the future of medicine (he could have added the future of surgery) depends.

The current trend among leaders in surgical research toward exploring the *normal* function of all organs, cells, and tissues could be illustrated by current work in a number of medical schools. In these centers, the problems of surgical patients (including such obvious surgical problems as nutrition and management of infection) are seen in terms of metabolic, respiratory, and circulatory balance, integrity of cardiac, pulmonary, and liver function. There is not a moment in which the surgeon can lose sight of the status of his patient's metabolic balance, that "nice balance between the rates of synthetic, in general energy-consuming processes and degradative, usually energy-yielding, reactions." The surgeon must maintain this balance under the assault of disease and operative trauma, must restore mechanisms of regulation and adaptation to a new balance, still conforming with the inherent nature of the organism. The knowledge upon which this ability rests derives from basic work on normal mechanisms, often carried on without specific clinical goals in view.

Some of the research now going forward in surgical laboratories has, it is true, owed its origin to hypotheses suggested by the surgeon's observation of postoperative or preoperative phenomena. Observation of necrosis of the liver, for instance, following various hepatoxic agents, a condition apparently associated with fat in the liver and the amount of protein available to the organism, led to well known biochemical studies of liver injury and liver repair, including studies of hypoproteinemia and of lipotropic factors. Observation of delayed wound healing years ago by Harvey of Yale led to his investigation of the velocity of growth of fibroblasts in wound healing (and tissue growth) and to in vitro studies of the influences of various substances on the growth of fibroblasts and on epithelialization. In sum, the problems of the surgical patient, as *Medical Research* clearly illustrates, involve many areas of fundamental, biologic research on normal mechanisms.

The content of the two volumes in brief review. The first volume of *Medical Research*, in an introductory chapter, describes how medicine, as a "free-wheeling eclectic" is steadily progressing toward an exact science through the impact of biology, chemistry and physics, mathematics, and atomic energy. The second chapter discusses the nature of research, the advantages and disadvantages of organizing research and of research "teams," the financing of research, the "climate" that favors basic research, the relation of science and the scientist to society. The long third chapter concretely illustrates basic research pertinent to medicine in each of the various types of agency: universities, medical schools, research institutes, foundations, industrial organizations, scientific societies, national voluntary health associations, governmental departments and divisions, including the federal research institutes, the National Academy of Sciences-National Research Council, the Atomic Energy Commission, and the National Science Foundation. Reports of current investigative work furnished the Foundation by these agencies were in many cases prepared especially for this survey. The last chapter of the first volume deals with the ways and means of making the results of research available—the scientific literature, conferences and symposia, indexing, and abstracting. The chapter discusses government control of the commercial products of research, the standardizing influence exercised by professional groups (as the American College of Surgeons and the American Medical Association's Councils), and the influence of patents in controlling the products of medical research.

The second volume, by a very different procedure, illustrates lines of basic research that are pertinent to solution of concrete clinical problems. An introductory chapter outlines the major biologic and metabolic concepts that are essential to understanding the normal mechanisms operating in health and the disturbed mechanisms that constitute disease. The 9 chapters that follow discuss 9 clinical conditions selected mere-

ly to illustrate the general truth that fundamental research in molecular biology is essential to solution of all clinical problems. The 9 illustrations are: cancer, infertility, arteriosclerosis, hypertension, rheumatic syndromes, tuberculosis, virus diseases (from fever blisters and the common cold to poliomyelitis and smallpox), chronic alcoholism, and schizophrenia. In addition to stressing the lines of fundamental research that give most promise of shedding light on the given problem, each chapter indicates the present gaps in biologic knowledge and the urgent need of bridging some of them as a condition of further advance.

Cancer and infertility. Space permits me to touch briefly upon the lines of basic research illustrated in only 2 chapters (which, however, may be the chapters of especial interest to surgical readers), cancer and infertility. No one knows better than the surgeon that extirpation of cancer tissue is not the complete answer, which can come only from fundamental knowledge of the causes of malignant change. In probing the reasons why an orderly normally growing cell becomes an outlaw and cancerous cell, the cancer chapter deals with basic work on factors that influence growth, normal and abnormal. Illustrating four interrelated approaches to study of malignant change, the chapter discusses work on chemical carcinogens, on hormones, on enzymes and nucleoproteins, and on viruses. The whole discussion is oriented by the view that the rational approach to clinical cancer requires more fundamental investigation of the nature of malignant change in terms of molecular alteration or metabolism.

Infertility, as discussed in the chapter under that head, ranges from complete sterility to various degrees of depressed fertility in either partner; it includes the still unknown factors responsible for untimely terminations of pregnancy, untimely initiation of labor, and the problem of congenital defect in offspring. It may be added in passing that it is to surgery that we owe, in recent decades, advances beyond the former merely descriptive analysis of congenital defect. Surgical correction of cardiac defects, once not compatible with life, has indeed stimulated hope that further basic research in fetal physiology may ultimately make it possible to deal with other congenital defects not now accessible to surgery. The inadequacy of present research in this whole field is deplored by J. P. Greenhill (Editor, *Year Book of Obstetrics and Gynecology*), who stresses the disparity between the "millions spent on such conditions as cancer and poliomyelitis" and the funds available for investigating such outstanding problems in our present civilization as sterility, fetal and neonatal deaths, and congenital defects.

Undoubtedly related to the problem of congenital defect are the many problems of reproductive physiology concerning the nature, nutrition, and metabolism of the germ plasm, the chemical mechanisms involved in fertilization. In addition to the two traditional schools of medical thought, one inclined to blame congenital defects on "defective germ plasm," the other inclined to consider the maternal environment of the embryo a more important factor, the infertility chapter mentions a third view: that only fundamental exploration of both the genetic and the physiologic problems will ultimately define the causes of congenital defect. Even if such research requires generations, progress in it will clarify many contributing factors and orient research by clearer separation of physiologic (presumably controllable) factors from genetic.

The infertility chapter well illustrates the point I stressed earlier, that the fundamental biologic research pertinent to any given clinical condition is likely to be pertinent also to other only apparently different conditions. Basic findings in cellular biology relevant to human infertility lie in exactly those areas of biology, biochemistry, endocrinology, neurology, and genetics from which are drawn also basic concepts related to cancer, virus and microbiology generally, and cardiovascular diseases.

Surgical problems touched upon incidentally in other chapters of Medical Research. There are at various points throughout the two volumes incidental references to subjects of especial interest to surgeons. These include: the subtle mechanisms of anesthesia, in need of a great deal of further research; the mechanisms of chemotherapy and of the antibiotics, use of which must be guided by further fundamental work in cellular biology if specific organisms are to be aimed at and if emergent resistant strains are to be understood; the future possibilities of radioactive isotopes, as in revolutionizing diagnosis through precise measurements of enzyme systems; and the genetic effects of radiation, now under more or less world-wide review.

Since the concern of *Medical Research* is always with fundamental causes and not with therapies, surgical procedures are mentioned chiefly as they seem to be related to fundamental physiologic mechanisms. It is noted, for instance, that the modern surgery of tuberculosis, which has dramatically changed the tuberculosis picture in recent years, applies a primary physiologic principle in substituting local tissue rest for the generalized rest of older therapies. There is no discussion of surgical intervention in the chapter on arteriosclerosis. The implication is that knowledge of the physiologic basis of this condition (its relation to the metabolism of all lipids and not merely cholesterol, and to such factors as antecedent arterial injury) is still inadequate to guide surgical intervention. The chapter on hypertension touches upon work on experimental renal hypertension, but it is pointed out that clinical counterparts of experimental renal hypertension are rare. The chapter discusses briefly experimental neurogenic hypertension and therapeutic sympathectomy but notes the doubts of many investigators as to whether it has contributed significantly to elucidating neural mechanisms in hypertension and as to whether there is any real distinction between sympathectomy (or, for that matter, drug therapy) and other nonspecific remedies.

In the chapter on the biology of schizophrenia, there is a brief discussion of attempts—regarded by some as premature—to apply current neurophysiologic knowledge to brain surgery in mental illness. The neurophysiologic observations and theories that underlie therapeutic "psychosurgery" are reviewed: Fulton's and Jacobsen's observation in 1935 of favorable changes in chimpanzees following ablation of the frontal association areas; application of these experimental results to humans by Moniz; use of the Moniz technique by Freeman and Watts, in prefrontal leucot-

omies in patients suffering frequent relapses into the psychotic state; and the development of various modifications of the Moniz technique (the lateral transcranial operation, the less drastic procedures, such as transorbital lobotomy, topectomy, and thalamostereotomy). Views of various workers are cited, stressing the lack of adequate study as yet of any of the 20,000 persons who have been subjected to psychosurgery.

Admitting that psychosurgery has been able to make obstreperous patients institutionally manageable (there are claims that it will abolish violent wards), some workers, nevertheless, feel that the "deconditioning of aggressivity" achieved by these operations amounts only to "a highly stereotyped mode of living" —in other words, a changed personality without sufficient initiative for normal living. *Medical Research* includes Kenneth Livingston's observation (on the basis of experimental work especially concerned with representation of autonomic functioning in the back part of the frontal lobe) that "in spite of extensive experiments with modified forms of the lobotomy procedure, the minimal effective anatomical lesion has not been defined, and the psychological basis for the operation has not yet been clearly established."

I commend *Medical Research* to my fellow surgeons for its consistent recognition that the future of medicine and of surgery depends upon basic physiologic perspective. The surgeon and the physician aim at *total* functional restoration; but perhaps the surgeon, even more concretely than the physician, knows that often all that is open to him is to substitute a lesser aberration for a greater one. Those of us who are daily chastened by this realization inevitably rest our hope of developing progressively better methods of surgical attack upon achieving more fundamental insight than is now available into the nature of biologic phenomena.

—*William S. Kiskadden.*

As one thumbs through the pages of the handsome new twenty-sixth edition of Gray's *Anatomy of the Human Body*,[2] edited by Professor Charles Mayo Goss of the Louisiana State Medical School, recollections of student days and one's first acquaintance with textbooks of anatomy flash across one's memory, and, less vividly, pictures of the many distinguished editors of earlier editions and, in the dim, background, visions of the many generations of medical students who since 1858—almost 100 years—pored over Gray's *Anatomy* as they strove to grasp and retain the details of form and structure of the human body.

The autobiography of one of them—Franklin H. Martin, the founder of this Journal—tells graphically in *The Joy of Living* of his initiation into his medical studies. His preceptor "went to the bookcase and after a long search brought out an old Wilson's 'Anatomy,' blew the dust off the yellow leather cover, and said, 'Learn what is in that, and occasionally I will quiz you.' I began with the first chapter on bones, and committed it word for word, commas, semicolons, periods, the dotted i's, and the crossed t's. I could begin at any paragraph and recite it verbatim.

"One day, he turned to me and said, 'Frank, what is the antrum of Highmore?' I told him.

" 'What bones enter into its formation? Can you bound it?' Without hesitation I began. With exactness I proceeded to bound this cavity, described in detail each notch, each foramen, each ridge, as they completed the mosaic of the antrum. When I was well started, he quietly sat up and gazed at me, and leaned forward with his hands resting on his knees. When I finished, in great astonishment he said, 'My God!' and got up and left the office. A few days afterward he brought me Gray's *Anatomy;* and said, 'This is an extra one, and you may keep it as your own.'

"It was my first possession in the way of a medical book. It was a large, leather-covered book, stained by wear, and in six months I knew its contents word for word. Never did a preceptor give more valuable advice to a student of medicine than Dr. Spalding gave to me as he impressed upon me that I was not simply to read, but that I must learn the human anatomy word for word, and in its entirety."

Whether Henry Gray, "who learned his anatomy by the slow but invaluable method of making dissections for himself," or William Harvey, who professed "to learn and to teach Anatomy, not from books but from dissections; not from the positions of philosophers but from the fabric of Nature" would have approved of Franklin Martin's method is doubtful but at least his generation did not "sail an uncharted sea." ("To study the phenomena of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all."—William Osler.)

It is impossible in a few paragraphs to give adequate recognition to the efforts that have been expended in revising and improving a monumental work such as Gray's *Anatomy*. Dr. Goss points out in his Preface some major changes in arrangement that have been made, such as bringing the chapter on surface anatomy to the beginning of the volume (Chapter II), including the nose with the respiratory system instead of with the organs of the senses, and giving to the heart a separate chapter. Since he has stated that the major revision in this edition has been made in the peripheral nervous system this section has been read with particular interest. It is exceedingly well done. The visceral nervous system and its relation to the cranial nerves and spinal nerves are described with unusual clarity, and throughout the section diagrams and illustrations, many of them in color, help to clarify what is often a confused and puzzling picture, certainly to the beginner in anatomy.

In this edition the comprehensive term, "visceral nervous system," is used to designate "the whole complex of fibers, nerves, ganglia, and plexuses by means of which impulses are conveyed from the central nervous system to the viscera and from the viscera to the central nervous system." The term "sympathetic system . . . is used in the restricted meaning of the thoracolumbar division of the visceral efferent system." Throughout the chapter, and particularly, in the section devoted to the visceral nervous system there are frequent references to the contributions of other workers, and at the end of the chapter a list of approximately 100 references to contemporary literature. Par-

[2] Anatomy of the Human Body. By Henry Gray, F.R.S. 26th ed. Edited by Charles Mayo Goss, M.D. 1480 pages, 1202 illustrations. $16.00. Philadelphia: Lea & Febiger, 1954.

ticularly in this chapter and in Chapter II, "Surface and Topographical Anatomy," many new and excellent illustrations, including a considerable number of reproductions of roentgenograms and a number of beautiful illustrations in color from Töndury's *Angewandte und topographische Anatomie*, have been added to bring both helpful understanding and new attractiveness to this twenty-sixth edition of Gray's great contribution to medical science. —*Sumner L. Koch.*

THE GERMAN VOLUME entitled *Grundriss und Atlas der gynaekologischen Cytodiagnostik*[3] fills a real need because for a long time German gynecologists and pathologists were skeptical of the great value of cytology. It was not until 1953 that the first symposium on cytology was held (in Heidelberg) by German cytologists interested in gynecology. This book is analogous to the well known books on cytology written in English by Papanicolaou and Traut, Ayre, and de Allende and Orias. It was prepared for the purpose of teaching the fundamentals of gynecologic cytodiagnosis and is based on the authors' experience with about 35,000 smears.

The first chapter consists of a very thorough review of the contributions made in cytology by investigators all over the world. In the following chapters the authors discuss the technique of obtaining and staining smears, the morphology of normal cells, the appearance of cells at different ages, changes in the cells due to pregnancy, the puerperium and abortion, differences in cells produced by inflammatory and other gynecologic disorders, the diagnosis of carcinoma, cell changes due to radium and roentgen radiation, cytodiagnosis from ascitic fluid, cytologic investigations by means of the phase contrast microscope, and organization of clinical cytodiagnosis.

There are 268 illustrations of which 186 are in color. All are beautiful and instructive. At the end of the book is a complete list of references on cytodiagnosis.

The authors are to be complimented on having produced such an excellent book. The publishers, too, deserve great credit, but the price set on the book may prevent its widespread sale. —*J. P. Greenhill.*

THE SMALL PAMPHLET, *Retrolental Fibroplasia*,[4] contains a surprising amount of recent information on one of the most fascinating diseases in the history of medicine. Retrolental fibroplasia is one of that unfortunate group of man's ills that are commonly called iatrogenic. It is fascinating in that the disease appeared, became almost epidemic in proportions, and that its cause was found and eliminated in a period of less than 2 decades. Retrolental fibroplasia was first described by Terry in 1942 and very shortly thereafter an intense study was made of the various elements in the management of prematures. Among the many things implicated at one time or another were anoxia, vitamin A, vitamin E, iron, and "intrauterine infection." Through the combined efforts of workers in this country, England, and Australia, the true villain, oxygen, was finally uncovered.

This manual gives the results of the most recent investigations on the mechanism of oxygen poisoning of the retina and points out how in an endeavor to salvage a greater number of premature infants a life-saving procedure became the most common cause of blindness in children. A short discussion of retinal metabolism and the probable site of the deleterious action of oxygen enhances the value of this booklet. —*David Shoch.*

A ROENTGENOGRAPHIC STUDY of the joints of the extremities is presented in the form of a monograph entitled *The Joints of the Extremities*.[5] It contains descriptions of methods and ideas which are not routine and illustrates some of the less common pathologic conditions.

The author was formerly director of the department of radiology and consultant in roentgenology at the Hospital for Special Surgery in New York. He shows that, with the exception of meniscus injuries, pathologic conditions of soft tissues can be diagnosed without the injection of a contrast medium.

The normal anatomy of soft tissue is shown by roentgenograms as well as with drawings. There are some excellent demonstrations of synovitis of the knee. Interarticular and extra-articular soft tissue disease is demonstrated by roentgenograms and drawings, and a good x-ray differential diagnosis is given.

In addition to the common conditions, many of the rare conditions are clearly demonstrated and discussed.

The monograph contains 102 plates with beautiful, well-defined, and clear illustrations. This book is a joy to any orthopedist. —*Emil D. W. Hauser.*

IN THE 836 PAGES which comprise the volume entitled *Experimental Surgery*,[6] the author, J. Markowitz, has 32 interesting chapters. These include not only discussions of major surgical procedures used in the laboratory but also a chapter on surgical exercises "suitable for undergraduate medical students," a provocative introductory chapter which should be a "must" for all concerned with medical education, plus an epilogue containing a valuable philosophy for improving medical education.

No review can adequately describe the material covered. The author concerns himself with such subjects as the antivivisection movement, care and feeding of animals, anesthesia, equipment, sutures and instruments, even illustrating the tying of knots. The surgical exercises represent a medical teaching Utopia which is seldom, if ever, achieved in graduate medical training, let alone undergraduate education. Exer-

[3] GRUNDRISS UND ATLAS DER GYNAEKOLOGISCHEN CYTODIAGNOSTIK. By H. Smolka and H. J. Soost. With a foreword by E. Philipp. 166 pages, 286 illustrations. DM 120.—$28.55. Stuttgart: Georg Thieme Verlag, 1956.

[4] RETROLENTAL FIBROPLASIA; ROLE OF OXYGEN. Report of the Sixteenth M & R Pediatric Research Conference. 62 pages, 20 illustrations. Issued by M & R Laboratories, Columbus, Ohio. 1955.

[5] THE JOINTS OF THE EXTREMITIES; A RADIOGRAPHIC STUDY. Notes on Non-routine Methods, Non-routine Ideas, and Less-common Pathology. By Raymond W. Lewis, M.D. 108 pages, 102 illustrations. $8.50. Springfield, Ill.: Charles C. Thomas, 1955.

[6] EXPERIMENTAL SURGERY; INCLUDING SURGICAL PHYSIOLOGY. By J. Markowitz, M.B.E., M.B.(Tor.), Ph.D., M.S. in Exp. Surg. (Minn.). In collaboration with J. Archibald, D.V.M., M.V.Sc., and H. G. Downie, D.V.M., M.S. (Cornell), M.V.Sc. 3rd ed. 851 pages, 554 illustrations. $10.00. Baltimore: The Williams & Wilkins Co., 1954.

cises of this type should be the goal of all surgical residencies.

After Chapter 7, "Standard Technical Procedures in the Surgery of the Alimentary Canal," there follows a chapter on peritonitis which may be recommended to all who invade the peritoneal cavity. Next come chapters on liver and biliary surgery, transplantation of organs, surgery of bones, joints, lungs, heart, and most of the important structures and organs. Repeated references to the basic sciences are combined with the discussion of experimental surgery for the ultimate goal of better surgical therapy.

In the Foreword, Best states: "This book is almost alone in its field," and "Experimental surgery as here presented is a branch of physiology, not the kind that deals with physics and chemistry of living tissue, but the sort that helps to correlate the structure of an organ with its gross function." This objective is achieved and medical students, practicing clinicians, medical faculty, and veterinarians can all use this text with profit.

The author is to be congratulated for this classic contribution to medical education.

—*S. J. Fogelson.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

Ankylosing Spondylitis; Clinical Considerations, Roentgenology. Pathologic Anatomy, Treatment. By J. Forestier, M.D., F.A.C.R. (Hon.), F. Jacqueline, M.D., and J. Rotes-Queroi, M.D. Translated by A. U. Desjardins, M.S., M.D., F.A.C.P., F.A.C.R. 374 pages, 145 illustrations. $10.75. Springfield, Ill.: Charles C. Thomas, 1956.

Das Hirntrauma; Beitraege zur Behandlung, Begutachtung und Betreuung Hirnverletzter. By Dr. Med. E. Rehwald. 527 pages, 106 illustrations. DM 44. $10.50. Stuttgart: Georg Thieme Verlag, 1956.

Pulmonary Carcinoma; Pathogenesis, Diagnosis, and Treatment. Edited by Edgar Mayer, M.D., and Herbert C. Maier, M.D. 540 pages, 182 illustrations, some in color. $15.00. Distributed by J. B. Lippincott Co., New York and Philadelphia. New York: New York University Press, 1956.

First Studies in Anatomy and Physiology. By John Cairney, D. Sc., M.D., F.R.A.C.S., and John Cairney, B.Sc., M.B., Ch.B. 205 pages, 103 illustrations. New Zealand price 30/—. Christchurch, New Zealand: N. M. Peryer Limited, 1956.

Hunterdon Medical Center; the Story of One Approach to Rural Medical Care. By Ray E. Trussell. 236 pages, 9 illustrations. $3.75. Cambridge, Mass.: Published for the Commonwealth Fund by Harvard University Press, 1956.

Scalpel; Men Who Made Surgery. By Agatha Young. 311 pages. $5.00. New York: Random House, 1956.

Harnableitung in den Darm; Uretero-Sigmoidostomie und Darm-Ersatzblasenbildung. By Prof. Dr. H. Boeminghaus. 59 pages, 57 illustrations. DM 15. $3.60. Stuttgart: Georg Thieme Verlag, 1956.

Cancer; a Manual for Practitioners. 3rd ed. 1956. 321 pages. $2.00. Boston, Mass.: Published by the American Cancer Society (Massachusetts Div.), Inc., 1956.

Thoracic Surgery for Physiotherapists. By Gladys M. Storey, S.R.N., F.C.S.P. With a foreword by N. R. Barnett, M.Chir., F.R.C.S. 132 pages, 31 illustrations. $3.00. Philadelphia: J. B. Lippincott Co., 1956.

A Search for Similarities. By Sir James Learmont, K.C.V.O., C.B.E., Ch.M., Ll.D., F.R.C.S.E. The ninth Macewen Memorial Lecture delivered in the University of Glasgow on April 15, 1955. 34 pages. Price: 5/—net. Glasgow: Jackson, Son & Co., Publishers to the University, 1956.

Modern Trends in Orthopedics. (Second Series.) Edited by Sir Harry Platt, Ll.D., M.D., M.S., F.R.C.S., F.A.C.S. 331 pages, 226 illustrations. $12.50. New York: Paul B. Hoeber, Inc., Medical Book Dept. of Harper & Bros., 1956.

A Pictorial History of Medicine. By Otto L. Bettmann, Ph.D. With a foreword by Philip S. Hench, M.D. 318 pages, illustrated. $9.50. Springfield, Ill.: Charles C. Thomas, 1956.

Handbook of Physical Therapy. By Robert Shestack, Ph.G.R.P., P.T.R. Foreword by I. William Nachlas, M.D. 212 pages, illustrated. $4.25. New York: Springer Publishing Co., 1956.

Der Fersenschmerz; funktionelle und organische Stoerungen im Bereich der Ferse und Achillessehne. By Prof. Dr. K. Stucke. 163 pages, 68 illustrations. DM 29.70. Stuttgart: Georg Thieme Verlag, 1956.

Chirurgie der grossen Koerpervenen. By Prof. Dr. med. R. Wanke, Prof. Dr. med. H. Junge, and Doz. Dr. med. H. Eufinger. 139 pages, 71 illustrations. DM 27. Stuttgart: Georg Thieme Verlag, 1956.

The Management of Menstrual Disorders. By C. Frederic Fluhmann, B.A., M.D., C.M. 350 pages, 121 illustrations. $8.50. Philadelphia and London: W. B. Saunders Co., 1956.

The Office Assistant; in Medical or Dental Practice. By Portia M. Frederick and Carol Towner. 351 pages, 55 illustrations. $4.75. Philadelphia and London: W. B. Saunders Co., 1956.

The Sequelae of Amputation. A Report of an Investigation. By Keith C. Bradley, F.R.A.C.S. 236 pages. Australia: Trustees of Services Canteens Trust Fund, 1955.

Operative Surgery of the Dog. By Joseph M. Miller, M.D., F.A.C.S., and Jeannette M. Whitehorn, A. B. Special Edition, Veterinary Bulletin. 64 pages, 30 illustrations. Pearl River, N. Y.: Lederle Laboratories Div., American Cyanamid Co., 1956.

The Doctor in Personal Injury Cases. By Harold A. Liebenson. 123 pages. $4.00. Chicago: The Year Book Publishers, Inc., 1956.

Annual Review of Medicine. David A. Rytand, Editor, and William Creger, Associate Editor. Vol. VII. 611 pages. $7.00. Stanford, Calif.: Annual Reviews, Inc., 1956.

AMERICAN COLLEGE OF SURGEONS

WARREN H. COLE, Chicago, *President*
DANIEL C. ELKIN, Lancaster, Kentucky, *President-Elect*

PRELIMINARY PLANS FOR THE 42nd CLINICAL CONGRESS THE CIVIC AUDITORIUM, SAN FRANCISCO, CALIFORNIA OCTOBER 8 TO OCTOBER 12, 1956

BOTH THE JUNE AND JULY ISSUES of this Journal have carried preliminary news about the Clinical Congress program. More details of the meeting are listed here, with the complete program to be announced in the September issue.

Postgraduate Courses

Courses will be presented Monday through Thursday, with the exception of the course on Gynecology and Obstetrics, which will be given Monday through Friday. All courses are scheduled from 8:30 to 11:30 a.m. and the fee is $5.00 per course. Registration is permissible for one course only. Because seating will be limited and these classes are so popular, it is wise to register as soon as possible. As an added convenience, your course ticket will be mailed to you in advance. The list of courses and chairmen follows:

Preoperative and Postoperative Care. HENRY THOMAS RANDALL, New York.
Gastrointestinal Tract. WILLIAM P. LONGMIRE, JR., Los Angeles.
Diseases of the Liver, Biliary Tract, and Pancreas. J. ENGLEBERT DUNPHY, Boston.
Cardiovascular Surgery. F. A. SIMEONE, Cleveland.
Fractures and Dislocations. FLOYD H. JERGESON, San Francisco.
Obstetrics and Gynecology. PHILIP H. ARNOT, San Francisco.
Orthopedic Surgery. FREDERIC C. BOST, San Francisco.
Surgical Aspects of Pulmonary Disease. PAUL C. SAMSON, Oakland.

Forum on Fundamental Surgical Problems

Sixteen Surgical Forum sessions will be held, morning and afternoon of each day of the Congress week, with one or more sessions for five special fields of surgery. The complete list of reports will be published in the next issue of this Journal.

General Sessions

General sessions will begin promptly at 10 a.m. on Monday morning. An outline follows:

MONDAY, 10 a.m.—Surgery of the Adrenal Glands. Moderator: OLIVER COPE, Boston. Collaborators: PETER H. FORSHAM, San Francisco; JAMES T. PRIESTLEY, Rochester, Minnesota; HAROLD A. ZINTEL, New York. 1:30–3 p.m.—Prophylaxis in Dissemination and Implantation of Cancer. Moderator: WARREN H. COLE, Chicago. Collaborators: LAUREN V. ACKERMAN, St. Louis; RUPERT TURNBULL, Cleveland; JOHN M. WAUGH, Rochester, Minnesota; FRANK C. WHEELOCK, JR., Brookline, Massachusetts. 3:30–5 p.m. — Hyperthyroidism. Moderator: HENRY H. SEARLS, San Francisco. Collaborators: RICHARD B. CATTELL, Boston; PAUL STARR, Los Angeles.

TUESDAY, 1:30–3 p.m.—Pelvic Pain in Women. Moderator: LANGDON PARSONS, Boston. Collaborators: OTTO AUFRANC, Boston; LAMAN A. GRAY, Louisville; KARL H. MARTZLOFF, Portland, Oregon; HENRY M. WEYRAUCH, San Francisco. 2–5 p.m. —Symposium on Trauma: Craniocerebral Injuries. EVERETT G. GRANTHAM, Louisville; Injuries to the Face and Neck. PAUL W. GREELEY, Chicago;

Injuries to the Thorax. PAUL C. SAMSON, Oakland; Injuries to the Abdomen. HOWARD E. SNYDER, Winfield, Kansas; Injuries to the Soft Tissues of the Extremities. OSCAR P. HAMPTON, JR., St. Louis; Injuries to the Skeletal System. JAMES K. STACK, Chicago; Priorities in Treatment. JOSEPH R. SHAEFFER, Washington, D. C. 3:30–5 p.m.—Surgical Management of Duodenal Ulcer. Moderator: JONATHAN E. RHOADS, Philadelphia. Collaborators: JAMES D. HARDY, Jackson, Mississippi; HENRY N. HARKINS, Seattle; RICHARD WARREN, Boston; DONALD R. WEBSTER, Montreal.

WEDNESDAY, 1:30–3 p.m.—Hiatal Hernia and Esophagitis. Moderator: STUART W. HARRINGTON, Rochester, Minnesota. Collaborators: MR. PHILIP R. ALLISON, Cambridge, England; ROBERT C. LAIRD, Toronto; HERBERT W. SCHMIDT, Rochester, Minnesota; JOHN M. DORSEY, Evanston. 2–5 p.m.—Symposium on Cancer. DANELY P. SLAUGHTER, *Presiding*. Explanation of Cancer Program of the American College of Surgeons. DR. SLAUGHTER; Review of Current Status of Chemotherapy. JOSEPH H. BURCHENAL, New York; Principles and Technique of Soft-Part Resection for Sarcomas. LEMUEL BOWDEN, New York; Biometric Evaluation of Mammary Cancer. JOSEPH BERKSON, Rochester, Minnesota; Diagnostic Significance of Lateral Tumors in the Neck. IAN MACDONALD, Los Angeles. 3:30–5 p.m.—What Antibiotics Should We Use, and When? Moderator: CHAMP LYONS, Birmingham. Collaborators: WILLIAM T. FITTS, JR., Philadelphia; CLAYTON H. CROSBY, Regina, Saskatchewan; LOWELL A. RANTZ, San Francisco.

THURSDAY, 1:30–3 p.m.—Burns. Moderator: JOHN D. MARTIN, JR., Emory University. Collaborators: CURTIS P. ARTZ, Fort Sam Houston; TRUMAN G. BLOCKER, JR., Galveston; BOYD W. HAYNES, JR., Richmond, Virginia. 1:30–3 p.m.—Symposium on Graduate Training in Surgery and the Surgical Specialties. FREDERICK A. COLLER, Chairman. 3:15 p.m.—Oration on Trauma: The Treatment of Open Wounds. MICHAEL L. MASON, Chicago.

FRIDAY, 9–12 noon—What's New In Surgery? HARRIS B. SCHUMACKER, JR., Presiding.

Color Television

In addition to the notable television program, a half-hour symposium will be held each morning, from 11:30 to noon, dealing with presentation of scientific and experimental data relating to clinical problems. Charts, x-rays, and other visual materials will be used to make the subject matter as graphic as possible.

Operations, surgeons, moderators, and time of programs are presented in the following, with a more complete list of panel members to be announced in the next issue:

MONDAY, 9–11:15 a.m.—Thyroidectomy for Tumor. HENRY H. SEARLS, San Francisco. Moderator: BROWN M. DOBYNS, Cleveland. Panel: RICHARD B. CATTELL, Boston; EDGAR L. FRAZELL, New York. 11:30 a.m.–12 noon—Symposium: Surgical Aspects of Ammonia Intoxication. Moderator: JOHN A. SCHILLING, Oklahoma City. Collaborators: BEN EISEMAN, Denver; WORTHINGTON G. SCHENK, JR., Buffalo. 2–3:30 p.m.—Radical Mastectomy for Carcinoma. H. GLENN BELL, San Francisco. Moderator: J. GARROTT ALLEN, Chicago. Panel: HEDLEY ATKINS, London, England; LAUREN V. ACKERMAN, St. Louis.

TUESDAY, 9–11:30 a.m.—Aortic Thromboendarterectomy. EDWIN J. WYLIE, San Francisco. Moderator: MICHAEL E. DEBAKEY, Houston. Panel: F. JOHN LEWIS, Minneapolis; WILLIAM H. MULLER, JR., Charlottesville. 11:30 a.m.–12 noon—Symposium: The Management of Breast Carcinoma. Moderator: STUART W. HARRINGTON, Rochester, Minnesota. Collaborators: HEDLEY J. B. ATKINS, London; ROBERT S. STONE, San Francisco. 2–3:30 p.m.—Hiatus Hernia Repair. H. BRODIE STEPHENS, San Francisco. Moderator: K. ALVIN MERENDINO, Seattle. Panel: C. ROLLINS HANLON, St. Louis; JOHN C. JONES, Los Angeles. 3:30–5 p.m.—Common Duct Exploration. ORVILLE F. GRIMES, San Francisco. Moderator: ROBERT M. ZOLLINGER, Columbus. Panel: FRANK GLENN, New York; I. S. RAVDIN, Philadelphia.

WEDNESDAY, 9–11:30 a.m.—Combined Operation for Intraoral Malignancy. MAURICE GALANTE, San Francisco. Moderator: TRUMAN G. BLOCKER, JR., Galveston. Panel: DANELY P. SLAUGHTER, Chicago; FRANK MCDOWELL, St. Louis. 11:30 a.m.–12 noon—Symposium: Newer Methods of Urinary Diversion. Moderator: R. KENNEDY GILCHRIST, Chicago. Collaborators: WILLARD E. GOODWIN, Los Angeles; CHARLES C. HIGGINS, Cleveland. 2–3:30 p.m.—Gastric Resection. HORACE J. MCCORKLE, San Francisco. Moderator: FRANCIS D. MOORE, Boston. Panel: LESTER R. DRAGSTEDT, Chicago; HENRY N. HARKINS, Seattle. 3:30–5 p.m.—Ventral Herniorrhaphy. VICTOR RICHARDS, San Francisco. Moderator: GEORGE B. PACKARD, Denver. Panel: CHESTER B. MCVAY, Yankton, South Dakota; CALEB S. STONE, JR., Seattle.

THURSDAY, 9–11:30 a.m.—Colectomy. ROBERT A. SCARBOROUGH, San Francisco. Moderator: J. ENGLEBERT DUNPHY, Boston. Panel: CLARENCE DENNIS, Brooklyn; R. KENNEDY GILCHRIST, Chicago. 11:30 a.m.–12 noon—Symposium: Diagnosis and Treatment of Islet Cell Tumors. Moderator: HILGER PERRY JENKINS, Chicago. Collaborator: EDWIN H. ELLISON, Columbus. 2–3:30 p.m.—Intestinal Obstruction. Moderator: HENRY T. RANDALL, New York. Panel: CHARLES G. JOHNSTON, Detroit; MARK M. RAVITCH, Baltimore; OWEN H. WANGENSTEEN, Minneapolis.

FRIDAY, 9–11:30 a.m.—Open Reduction of Ankle. LEROY C. ABBOTT, San Francisco. Moderator: SAM W. BANKS, Chicago. Panel: EDWIN F. CAVE, Boston; J. SPENCER SPEED, Memphis. 11:30 a.m.–12 noon—Symposium: Portal Hypertension: Methods of Management. Moderator: WILLIAM P. LONGMIRE, JR., Los Angeles. Collaborators: JERE W. LORD, JR., New York; ROBERT R. LINTON, Boston; ROLLIN A. DANIEL, JR., Nashville. 2–3:30 p.m.—Surgical Correction of Hypospadias. DONALD R. SMITH, San Francisco. Moderator: FRANK HINMAN, JR., San Francisco. Panel: EDGAR BURNS, New Orleans; ARTHUR B. CECIL, Los Angeles.

Surgical Specialties

GYNECOLOGY AND OBSTETRICS

MONDAY, 1:30–3 p.m.—Panel: Indications and Techniques in Induction of Labor. Moderator: JAMES L. REYCRAFT, Cleveland. Collaborators: L. GRANT BALDWIN, Pasadena; BERNARD J. HANLEY, Los Angeles; J. BAY JACOBS, Washington, D. C. 3:30–5 p.m.—Panel: Metabolic Impact of Surgery. Radiation and Labor. Moderator: MILTON L. MCCALL, New Orleans. Collaborators: R. GLENN CRAIG, San Francisco; GILBERT J. VOSBURGH, New York; JOHN A. WALL, Houston.

TUESDAY, 1:30–3 p.m.—Panel: Pelvic Pain in Women. Moderator: LANGDON PARSONS, Boston. Collaborators: OTTO E. AUFRANC, Boston; LAMAN A. GRAY, Louisville, HENRY M. WEYRAUCH, San Francisco. 3:30–5 p.m.—Panel: Contrasted Methods in Treatment of Abruptio. Moderator: CONRAD COLLINS, New Orleans. Collaborators: STANLEY M. BYSSHE, New York; ROBERT M. KELLY, Riverside, California; CHARLES O. MCCORMICK, Indianapolis.

WEDNESDAY, 1:30–3 p.m.—Panel: Prematurity and Postmaturity. Moderator: RUSSELL R. DE ALVAREZ, Seattle. 3:15–5 p.m.—Surgical Forum Session.

THURSDAY, 1:30–3 p.m.—Panel: Perineal Trauma. Moderator: HAROLD L. GAINEY, Kansas City, Missouri. Collaborators: ROBERT H. BARTER, Washington, D. C.; ALBERT DECKER, New York; EMIL J. KRAHULIK, Los Angeles.

FRIDAY, 3:15–4:45 p.m.—Panel: Surgical Standards in Treatment of Carcinoma of the Cervix. Moderator: ERLE HENRIKSEN, Los Angeles. Collaborators: S. B. GUSBERG, New York, GEORGE F. MELODY, San Francisco; JAMES F. NOLAN, Los Angeles.

NEUROLOGIC SURGERY

THURSDAY, 9 a.m.–12 noon—Surgical Forum Session.

FRIDAY, 9–10:30 a.m.—Panel: Surgical Management of Intracranial Aneurysms and Arteriovenous Malformations. Moderator: RUSSELL MEYERS, Iowa City. Collaborators: WALLACE B. HAMBY, Buffalo; CARL F. LIST, Grand Rapids; FRANCIS MURPHEY, Memphis; J. LAWRENCE POOL, New York. 10:30 a.m.–12 noon—Panel: Surgical Management of Cerebrovascular Disease. Moderator: E. S. GURDJIAN, Detroit. Collaborators: EDWIN B. BOLDREY, San Francisco; H. J. SVIEN, Rochester, Minnesota; WILLIAM H. SWEET, Boston. 1:30–4:45 p.m.—Neurosurgery Symposium.

ORTHOPEDIC SURGERY

WEDNESDAY, 2–5 p.m.—Surgical Forum Session.

FRIDAY, 1:30–3 p.m.—Panel: Fractures of Tarsal and Metatarsal Bones. Moderator: E. GEORGE CHUINARD, Portland, Oregon. Collaborators: CHARLES W. GOFF, Hartford; RONALD S. HAINES, Phoenix. 3:15–4:45 p.m.—Panel: Differential Diagnosis and Treatment of Low Back Pain and Sciatica. Moderator: GUY A. CALDWELL, New Orleans. Collaborator: LEO S. LUCAS, Portland, Oregon.

OPHTHALMOLOGY

WEDNESDAY, 2–5 p.m.—Ophthalmology Symposium.

OTOLARYNGOLOGY

THURSDAY, 1:15–3:15 p.m.—Symposium: Mobilization of the Stapes in Otosclerosis. Moderator: HOWARD HOUSE, Los Angeles. Participants: SHIRLEY HAROLD BARON, San Francisco; RICHARD J. BELLUCCI, New York; VICTOR GOODHILL, Los Angeles; HOWARD P. HOUSE, Los Angeles; FRANCIS A. SOOY, San Francisco.

PLASTIC SURGERY

THURSDAY, 2–5 p.m.—Surgical Forum Session.

FRIDAY, 1:30–3 p.m.—Panel: Reconstructive Surgery of the Neck. Moderator: DONALD M. GLOVER, Cleveland. Collaborators: SIDNEY E. BLANDFORD, Denver; FRANK F. KANTHAK, Atlanta; HENRY S. PATTON, Oakland. 3:15–4:45 p.m.—Panel: Reconstructive Surgery of the Eyelids and Orbital Region. Moderator: WILLIAM S. KISKADDEN, Los Angeles. Collaborators: CLIFFORD L. KIEHN, Cleveland; DOUGLAS W. MACOMBER, Denver; DAVID W. ROBINSON, Kansas City, Kansas.

THORACIC SURGERY

FRIDAY, 1:30–3 p.m.—Panel: Selective Pulmonary Resection. Moderator: ROBERT R. SHAW, Dallas. Collaborators: J. MAXWELL CHAMBERLIN, New York; WILLIAM S. CONKLIN, Portland, Oregon; PAUL W. GEBAUER, Honolulu; ROBERT C. MAJOR, Augusta, Georgia. 3:15–4:45 p.m.—Panel: Recent Developments in Cardiac Surgery. Moderator: ALFRED BLALOCK, Baltimore. Collaborators: F. HENRY ELLIS, JR., Rochester, Minnesota; EMILE HOLMAN, San Francisco; WILLIAM H. MULLER, JR., Charlottesville, Virginia.

UROLOGY

MONDAY, 3:30–5 p.m.—Panel: Hypospadias. Moderator: EDGAR BURNS, New Orleans. Collaborators: ORMOND S. CULP, Rochester, Minnesota; DONALD R. SMITH, San Francisco.

TUESDAY, 1:30–3 p.m.—Panel: Evaluation of Isotopes in the Treatment of Carcinoma of the Prostate and Bladder. Moderator: VINCENT J. O'CONOR, Chicago. Collaborators: MARSHALL H. BRUCER, Oak Ridge; DAVID A. CULP, Iowa City; FRANK HINMAN, JR., San Francisco.

WEDNESDAY, 1:30–3 p.m.—Panel: Surgical Injuries of the Lower Urinary Tract. Moderator: WM. NILES WISHARD, JR., Indianapolis, Indiana. Collaborators: RALPH C. BENSON, Portland, Oregon; GRAYSON CARROLL, St. Louis; RUBEN H. FLOCKS, Iowa City.

THURSDAY, 9 a.m.–12 noon—Surgical Forum Session.

FRIDAY, 1:30–3 p.m.—Panel: Management of Obstructions of the Upper Urinary Tract. Moderator: REED M. NESBIT, Ann Arbor. Collaborators: THOMAS E. GIBSON, San Francisco; MILES GRIFFIN, Oakland; FRANK C. HAMM, Brooklyn; FREDERICK C. SCHLUMBERGER, Beverly Hills.

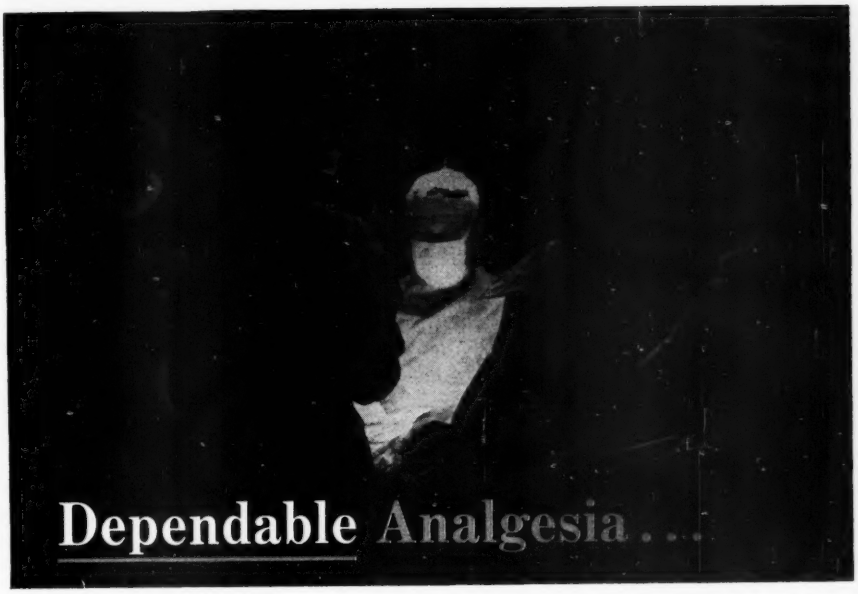
Special Guest Speakers

Dr. Vannevar Bush, distinguished scientist, will give the Martin Memorial Lecture on Monday evening. On Thursday afternoon Dr. Michael L. Mason will give the Oration on Trauma, speaking on "The Treatment of Open Wounds." On Friday evening Dr. Daniel C. Elkin will give the Presidential Address.

Advance Reservations

All official forms—advance registration, postgraduate courses, transportation, and hotel accommodations—must be obtained from The American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois. The advantages of advance registration are emphasized here again: you are handed your badge and tickets immediately on checking in, so that there is no waiting in line; you are more likely to obtain the postgraduate course of your choice, and your ticket is mailed to you in advance.

Fees, except for postgraduate courses, are not required of Initiates, Candidates, or Surgical Residents. Fellows whose dues are paid to December 31, 1955, do not pay a registration fee; those whose dues are not paid are charged $20.00. Non-Fellows pay $20.00, and members of the Federal Services pay $10.00. The postgraduate course fee is $5.00.



PROFOUND • PROLONGED • CONTROLLED

with Pontocaine®

hydrochloride

SADDLE BLOCK

0.2% Pontocaine HCl in dextrose (hyperbaric) ampuls of 2 cc. (4 mg.) Also "Niphanoid"® (instantly soluble dry form) and 1% solution in saline (isobaric)

SPINAL

HIGH
MEDIUM
LOW

0.3% Pontocaine HCl in dextrose (hyperbaric) ampuls of 5 cc. (15 mg.)
"Niphanoid," ampuls of 10, 15 and 20 mg.
1% solution (in saline) 2 cc. (20 mg.)

NERVE BLOCK AND INFILTRATION

0.15% solution, vials of 100 cc.
"Niphanoid," ampuls of 250 mg.

Pontocaine (brand of tetracaine) and Niphanoid, trademarks reg. U.S. Pat. Off.

Winthrop LABORATORIES
NEW YORK 18, N. Y. • WINDSOR, ONT.

with THORAZINE*

in Obstetrics—

fewer narcotized babies

Need for resuscitation reduced by more than 50%

In their series of 285 patients, Anz and Smith[1] observed that, when 'Thorazine' was administered with reduced amounts of the usual obstetric medication, the need for resuscitation of the newborn was decreased by more than 50 per cent

	WITH 'THORAZINE'	WITHOUT 'THORAZINE'
Deliveries	135	150
Babies requiring:		
Mild resuscitation†	8.1%	18.7%
Active resuscitation‡	- -	3.3%
Totals	8.1%	22.0%

'Thorazine' is available in ampuls, tablets and syrup (as the hydrochloride), and in suppositories (as the base).

1. Anz, U.E., and Smith, L.J.: Clinical Evaluation of Chlorpromazine in the Management of Labor, Am. J. Obst. & Gynec., in press.

Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.

Printed by R. R. Donnelley & Sons Co., Chicago, Illinois, U. S. A.